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FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC DRUG DELIVERY SYSTEM OF METOPROLOL SUCCINATE

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ABSTRACT

Controlled porosity osmotic tablet of Metoprolol succinate prepared and evaluated in this study. Metoprolol succinate is very low soluble drug. So it is difficult to formulate osmotic tablet of Metoprolol succinate which gives drug release up to 24 hr at zero order. To get desired dissolution profile various formulation parameters like osmogen concentration, level of weight gain and level of pore former concentration were studied. Final optimized formulation was studied for effect of pH of dissolution media, agitation. There is no effect of pH of dissolution media and agitation intensity on dissolution. There is significant effect of osmotic pressure on dissolution confirms that prepared metoprolol succinate tablet gives drug release with osmotic mechanism.

KEYWORDS: Metoprolol succinate, Controlled porosity osmotic tablet, Zero order

INTRODUCTION

Conventional drug delivery systems have little control over the drug release and so effective concentration at the target site cannot be achieved. This kind of dosing pattern may result in unpredictable plasma concentrations. But oral controlled drug delivery dosage forms provide desired drug release pattern for longer period of time and so the rate and extent of drug absorption from oral controlled drug delivery formulations can be predicated. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract[1]**.** But drug release from osmotic drug delivery system is not affected by physiological factors.

Controlled porosity osmotic tablet contains core tablet coated with semipermeable membrane which allows active agent to come outside through pores formed in situ[2]. The controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules, such as sodium chloride, potassium chloride, urea, and sucrose etc. into major component of film coating material[3]. These pore-forming agents are leached when contacted with an aqueous medium, and the pores are created on the surface to allow drug release. Plasticizer can also be used as pore forming agent. Plasticizer has been used to modify not only the mechanical properties but also the thermal property, water absorption behavior, and adhesive property of polymeric films[4,5].

The metoprolol succinate is an anti-hypertensive drug. Single oral administration of conventional 100 or 200 mg doses of metoprolol succinate produces peak plasma concentrations within 1.5-2 h of dosing, but by 24 h the drug is virtually cleared from plasma. Although conventional tablet formulations can be administered once daily in high doses, divided doses are required to maintain an even response over 24 h. This has lead to the development of slow-release formulations which permit therapeutic doses to be administered once daily while maintaining an acceptable clinical response throughout the dosage interval[6]. The existing polymer-matrix slow-release formulations are designed to reduce the peak concentration and sustain plasma levels for a longer period after dosing compared with conventional

rapid-release tablets have made it possible to develop improved formulations for once-daily use[7].

MATERIALS AND METHODS

Metoprolol succinate purchased from Dr Reddy's Laboratories Ltd. Sodium chloride, MCC-112, Polyvinylpyrrolidone PVPK -30, Magnesium Sterate, Talc, Mannitol, Cellulose acetate, Acetone, Triethyl citrate(TEC) . Sodium chloride (S. D. Fine chem., India) was used as osmogent and MCC (DMV, India) was used as diluent. Povidone (BASF Corporation, India) was used as binder and magnesium stearate (Ferro) was used as lubricant. Cellulose acetate with 39.8% acetyl content (Eastman chem., USA) was used as semipermeable membrane. Mannitol (Roquette feres) was used as pore former.TEC (Vertellus performance materials Inc) is used as plasticizer respectively. The other chemicals used were of analytical grade.

Method of Preparation :

bulk density determination: Weighed quantity of the powder (W) was taken in a graduated measuring cylinder and volume (V_0) was measured and bulk density was calculated using the formula. As show in table no 3

Bulk density (BD) = Weight of the powder/ Volume of powder

$$BD = W/V_0 \ g/mL$$

Tapped density determination: Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_0). The graduated cylinder was fixed in the 'Tapped Densiometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). As show in table no 3. The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

Tapped density (TD) = W g/ml

Angle of repose: Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. As show in table no 3. The angle of repose was calculated by using the formula given below.

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1}(h/r)$$

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose

Carr's index: Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics. As show in table no 3. Carr's index was calculated by using the formula:

$$\text{Carr's Index} = \frac{\text{(Tapped Density – Bulk Density)}}{\text{Tapped Density}} \times 100$$

Hausner ratio: Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property. As show in table no 3. Hausner ratio was calculated by using the formula.

Hausner Ratio = Tapped density / Bulk density

$$\text{Hausner Ratio} = V_f / V_0$$

Where V_0 = Initial volume

V_f = Final volume

Friability: This test is intended to determine under defined conditions, the friability of uncoated tablets, and the phenomenon whereby tablet surfaces are damaged and show evidence of lamination or breakage when subjected to mechanical shock or attrition. Commercially available apparatus known as "Friabilator" are used for the test. Basically, it consists of a drum with diameter between 283mm and 291mm and having width of 36 mm–40 mm, made of transparent plastic material. The drum is attached to the horizontal axis of a device that rotates at 25±1 rpm. The tablets are tumbled at each turn of the drum by a curve projection with an inside radius of 75.5 mm–85.5mm that extends from middle of the drum to outer wall. Thus, at each turn, the tablets roll or slide and fall onto the drum wall or onto each other. Usually, a sample of 10 tablets are tested at a time, unless tablet weight is 0.65 g or less, where 20 tablets are tested. After 100 turns, the tablet samples are evaluated by weighing. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test. As show in table no 3.

Usually, the test is performed during formulation development stage to as certine the tablet capacity to withstand shocks during transportation. If the tablets are cracked, cleaved or broken then the sample fails the friability test.

Hardness testing: A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping and dispensing. As discussed before, hardness and friability are most common measures used to evaluate tablet strength.

If a tablet is more fragile than expected, then the friability test will detect its substandard quality. If the tablets are more robust than desired, then tablet hardness test that will detect the deficiency. The most

widely used apparatus to measure tablet hardness is the Schleuniger apparatus. This, and other newer electrically operated test equipment, eliminates the operator variability inherent in the measurement using older apparatuses. Generally, the force required to break a tablet may be expressed in either kilograms or pounds. As show in table no 3.

Weight variation: Weigh individually 20 tablets than calculate the average weight by using following formula and the results as shown in table no.4
Average weight of tablets = sum of weight of 20 tablets/20
Calculate the standard deviation
S.D = (∑(x-x)2/n)1/2

Disintegration test: A disintegration test is a test to establish how fast a tablet disintegrates into aggregates and/or finer particle, the test is conducted using a specially designed instrument known as disintegration apparatus. The apparatus employs a basket of six tubes with a base of metal sieve. A tablet is placed in each tube and is held in place by a plastic weight. The six-tube assembly, containing six tablets, is suspended using a hanger with a mechanism of vertical motion at a fixed speed of 28-32cycles/minute. While hanging the six-tube assembly on the hanger, the assembly is moved in vertical motion in water or a buffer solution. The time for disintegration of each tablet is recorded and should meet the required time specification. As show in table no 3.

Dissolution: Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.
Dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behaviour of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between *in- vitro* dissolution rate of many drugs and their *in-vivo* bioavailability has been demonstrated and is generally referred to as *in-vitro in-vivo* correlation, IVIVC.

Dissolution Testing Conditions:

a. **Apparatus:** The most commonly employed dissolution test methods are

(1) The basket method (Apparatus 1) and

(2) The paddle method (Apparatus 2)

The basket and the paddle methods are simple, robust, well standardized and used worldwide. These methods are flexible enough to allow dissolution testing for a variety of drug products. Apparatus 1 and Apparatus 2 should be used unless shown to be unsatisfactory. The *in-vitro* dissolution procedures, such as the reciprocating cylinder (Apparatus 3) and a flow-through cell system (Apparatus 4) described in the USP may be considered, if needed. These methodologies or other alternatives/modifications should be considered on the basis of their proven superiority for a particular product. Because of the diversity of biological and formulation variables and the evolving nature of understanding in this area, different experimental modifications may need to be carried out to obtain a suitable *in-vivo* correlation with *in-vitro* release data. Dissolution methodologies and apparatus described in the USP can generally be used either with manual sampling or with automated procedures.

b. **Dissolution Medium:** Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to *in-vivo* performance of the product. However, strict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration.
The volume of the dissolution medium is generally 500, 900, or 1000 ml. Sink conditions are desirable but not mandatory. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers is given in USP) should be used.
To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0.
To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. Recent experience with gelatin capsule products indicates the possible need for enzymes (pepsin with SGF and pancreatin with SIF) to dissolve pellicles, if formed, to permit the dissolution of the drug. Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients. For water insoluble or

sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulphate is recommended. The need for and the amount of the surfactant should be justified. Use of a hydro alcoholic medium is discouraged.

All dissolution tests for IR dosage forms should be conducted at 37±0.5°C. The basket and paddle method can be used for performing dissolution tests under multimedia conditions (e.g., the initial dissolution test can be carried out at pH 1.2, and, after a suitable time interval, a small amount of buffer can be added to raise pH to 6.8). Alternatively, if addition of an enzyme is desired, it can be added after initial studies (without enzymes).

Use of Apparatus 3 allows easy change of the medium. Apparatus 4 can also be adopted for a change in dissolution medium during the dissolution run.

Certain drug products and formulations are sensitive to dissolved air in the dissolution medium and may need desertion.

c. Agitation:

In general, mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor *in-vivo* performance. Using the basket method, the common agitation (or stirring speed) is50-100 rpm; with the paddle method, it is 25-75 rpm. Apparatus 3 and 4 are seldom used to assess the dissolution of immediate release drug products.

Evaluation of Developed Formulations: Dissolution of coated formulation was carried out in three different phosphate buffers for a period of 24 hrs with apparatus USP II (paddle) method of 50 rpm and dissolution media was kept at 37±0.5 ºC. The samples were withdrawn (10ml) at different time intervals and replaced with 10 ml of fresh media. Samples were withdrawn at 1, 2, 4,6,8,12,18 and 24 hr for measurement of drug release. Samples were analyzed using UV spectrometer at 275nm. As show in table no 4.

Effect of membrane thickness: To study the influence of membrane thickness on drug release studies, the optimized elementary osmotic tablets were coated in the coating pan using semi-permeable polymer (Cellulose Acetate) 4% w/v in acetone using TEC at concentration of 10% of w/w of cellulose acetate, as plasticizer. The CPOP tablets were coated in a coater continuously until to get an increase in percent of membrane thickness (0.22, 0.39, and 0.51 mm respectively) over the core tablets to get different thickness (table 31). After getting different coat thickness over the core tablets, they were drilled to get know orifice whose size is determined. Release studies were conducted for the above made coated tablets with different thickness as shown in table no.5.

Effect of Agitation Intensity: To study the effect of agitation intensity on drug release, optimized formulation was subjected to dissolution at various rotation speeds. Dissolution was carried out in USP-II (Paddle) at 25, 50 and 75 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 275nm using UV spectrometer. As show in table no 6.

Effect of pH: To study the effect of pH on drug release, dissolution study was carried in dissolution media having different pH. Dissolution was carried in 900 ml of pH 1.2 acid buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Dissolution apparatus (USP-II) was used for drug release study at 50 rpm[8]. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 275nm using UV spectrometer. As show in table no 7.

Effect of Osmotic Pressure: The mechanism of drug release was studied based on osmotic pressure. To increase the osmotic pressure of the formulation, sodium chloride was added in different ratios (0%,0.25%,0.5%,0.75%,0.875%,1%) of formulations. Release studies were carried out in 900 ml of 0.1 N HCl using USP-II dissolution apparatus at 50 rpm. Effect of osmotic pressure created by formulations was evaluated by drug release at different intervals. As show in table no 8.

RESULTS AND DISCUSSION

Formulation Development: Osmotic tablet consist of core tablet coated with a rate controlling membrane. Core tablet consists of drug along with release retardant, osmogen and other conventional excipients to form the core compartment. The core tablet is surrounded by a membrane consisting of a semipermeable polymer and pore former cum plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane is permeable to aqueous fluids but substantially impermeable to the components of the core[8]. During operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The dissolved drug is released through the pores created after leaching of water soluble additive in the membrane. Cellulose acetate was used as water-insoluble polymer. PVP was used as binder TEC is used as plasticizer and mannitol as pore former.

Effect of Osmogen Concentration: To check the effect of osmogen concentration on drug release, formulations were prepared with different concentration of sodium chloride and all other parameters of tablet kept constant. Therefore it is concluded that drug release from prepared tablet was done through osmotic pressure[9,10]. Concentration of sodium chloride is required to be optimized to get the required release profile.

Effect of Pore Former Concentration: In controlled porosity osmotic pump, core tablet was coated with semipermeable membrane having pore former. After coming in contact with aqueous media, pore former dissolves and leaches out from the coating which creates microporous membrane around tablet. Drug release was done through these pores[11,12]. So concentration of pore former in controlled porosity osmotic pump is important parameter in controlling the release rate. Tablets were coated with different ratios of cellulose acetate/mannitol and subject to dissolution after sufficient weight gain achieved. Different concentration of mannitol (% of cellulose acetate) like 50%, 60% and 70% were tried. (Figure - 2).

By decreasing the concentration of pore former, drug release was decreased linearly. There is significant effect of poreformer concentration on drug release observed.

Effect of Coating Weight Gain: Core tablets were coated with semipermeable membrane of cellulose acetate with different weight gain to identify the effect of coating gain on drug release[13,14]. Core tablets were coated with 2%,4%, 6% and 8% weight gain and subject to dissolution. (Figure 3)
There is difference in dissolution observed with different weight gain tablets. With increase in coating weight gain, drug release rate decreased.

Performance Evaluation of Optimized Formulation: Final formulation was evaluated for various dissolution studies to check effect of pH, agitation intensity and osmotic pressure. In order to study the effect of pH on drug release, dissolution was carried out in media of different pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer in USP-II apparatus (Paddle) at 50 rpm. Drug release for optimized formulation was found similar in all three media. Optimized formulation shows pH independent drug release as per figure 4.

To study the effect of agitational intensity of the release media, release studies of the optimized formulation was carried out in USP dissolution apparatus type II at varying rotational speed (25,50, and 75 rpm) in 900 ml of 0.1 N HCl. It is clearly evident from figure 5 that the release of metoprolol succinate is independent of the agitation intensity[16]. Drug release in all three conditions found similar.

Release mechanism: The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (e.g. time) are mentioned as table no .9. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like R^2 regression coefficient value[17,18,19].

CONLUSION

Extended release formulations of Metoprolol succinate were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Solubility of active pharmaceutical ingredient is the key factor in development of osmotic dosage form. Effect of sodium chloride concentration, pore former concentration and weight gain of tablets on dissolution was also checked. Concentration of sodium chloride, pore former increases, dissolution rate of Metoprolol succinate also increases. But increase in the tablet weight gain is inversely proportional to the dissolution release rate.

The release from the optimized formulations was independent of pH and agitation intensity of the release media, assuring the release from the tablet was independent of pH and hydrodynamic conditions of the body. Metoprolol succinate release from the developed formulation was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release.

Table1: Formulation of tablets

Core composition						
INGREDIENTS	**Drug compartment composition, mg/core tablet (variable)**					
Batch no:	**F1**	**F2**	**F3**	**F 4**	**F5**	**F 6**
Ratio(M S :osmotic)	1:00	1:0.25	1:05	1:0.75	1:0.875	1:1
Metoprolol succinate	200	200	200	200	200	200
Sodium Chloride #100	0	50	100	150	175	200
Microcrystalline Cellulose-112	180	135	85	35	10	15
Polyvinylpyrrolidone-k-30	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Average weight	400	400	400	400	400	430

Table 2: Coating solution composition

INGREDIENTS	**WEIGHT**	**CONCENTRATION (%)**
Cellulose acetate	40gms	4%
Triethyl citrate	4 gms	0.4
Mannitol	Quantity sufficient	Quantity sufficient
Acetone	1000ml	Quantity sufficient

Table3: Evaluation of the pharmaceutical powders and tablets

PHYSICAL PARAMETER	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ratio(M S :osmotic)	1:00	1:0.25	1:05	1:0.75	1:0.875	1:01
Average weight(mg)	400	399.5	398.5	400	399.5	429
LOD%	1.05	1.04	1.02	1.12	1.98	1.6
Bulk density(gm/ml)	0.429	0.585	0.535	0.659	0.555	0.875
Tap density(gm/ml)	0.574	0.676	0.656	0.755	0.656	0.998
Carr's compressibility index %	25.3	13.4	18.3	12.5	15.1	12.3
Hausner Ratio	1.33	1.15	1.22	1.14	1.18	1.14
Friability %	1.029	0.014	0.014	0.073	0.2	0.043
Disintegration time(min)	18-20	8-9	2-3	1-1.5	1-1.5	1-2
Hardness(k_p)	20-21	16.5-17.5	16-17	10-11	7.5-8	7.5-8
Thickness (mm)	5.63	5.63	5.5	5.5	5.5	5.5

Table-4: Evaluation of coated formulation

physical parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ratio(M S :osmotic)	1:00	1:0.25	1:05	1:0.75	1:0.875	1:01
Average weight(mg)	398.5	400	400	401	399.5	399
Thickness(mm)	5.81	5.79	5.68	5.64	5.69	5.68

Table-5: Influence of membrane thickness on drug release profile

Cumulative percentage of drug release				
TIME	**2%**	**4%**	**6%**	**8%**
0	0	0	0	0
2	43	27	22	20
4	52	49	28	23
6	63	62	33	33
8	74	64	43	46
12	82	83	57	53
18	95	90	70	60
24	103	91	77	62

Table 6: Cumulative percentage of drug release

Time(Hr)	25rpm	50rpm	75rpm
0	0	0	0
1	2.2	2.6	3
2	5.3	5.5	6
4	8.6	9	9.3
6	12	12.9	14
8	23.5	24.9	26.9
12	38.6	40.3	42.7
18	65.6	68.4	72
24	88.2	90.9	93.5

Table 7: DISSOLUTION PROFILE ON INFLUENCE OF PH

Time	**pH 1.2**	**pH 4.5**	**pH 6.8**
0	0	0	0
2	11	13	15
4	20	19	18
6	32	29	30
8	41	39	44
12	60	58	63
18	80	77	79
24	93	92	96

Table 8: INVITRO DRUG RELEASE OF FORMULATION

S.NO	F1	F2	F3	F4	F5	F6
Drug:Osmogen	1:00	1:0.25	1:0.5	1:0.75	1:0.875	1:1
0	0	0	0	0	0	0
1	20±1.7	15±22.3	11±1.5	20±1.7	28±2.5	30±0.0
2	34±2.6	27±3.5	13±2.1	22±0.0	30±3.5	32±0.0
4	45±3.5	49±5.0	28±1.5	39±1.5	42±4.2	41±2.1
6	51±12.6	62±4.7	42±4.0	44±1.0	52±2.8	47±3.5
8	59±6.6	64±6.4	53±13.2	65±4.6	65±3.5	62±3.5
12	68±2.5	83±5.3	69±2.3	81±1.2	83±2.1	84±2.8
18	79±3.6	90±2.1	84±11.0	86±0.6	91±2.1	101±0.7
24	88±4.6	91±1.5	95±8.5	100±0.6	102±0.7	105±1.4

Table 9: **Release mechanism by mathematical models**

Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F1	0.701	0.953	0.915	0.944
F2	0.787	0.894	0.949	0.939
F3	0.938	0.903	0.974	0.798
F4	0.889	0.901	0.976	0.865
F5	0.870	0.911	0.979	0.973
F6	0.906	0.931	0.981	0.951

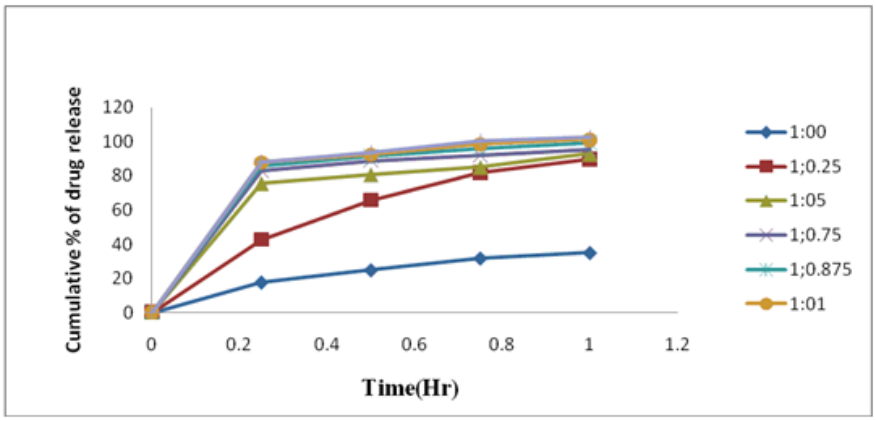

FIGURE 1: Effect of osmogen concentration

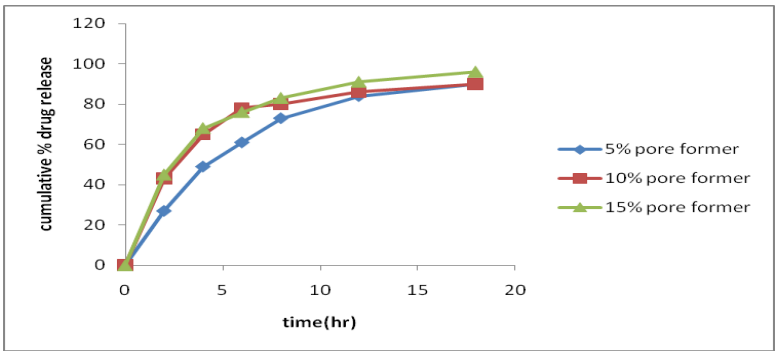

FIGURE 2 : Effect of Pore former concentration

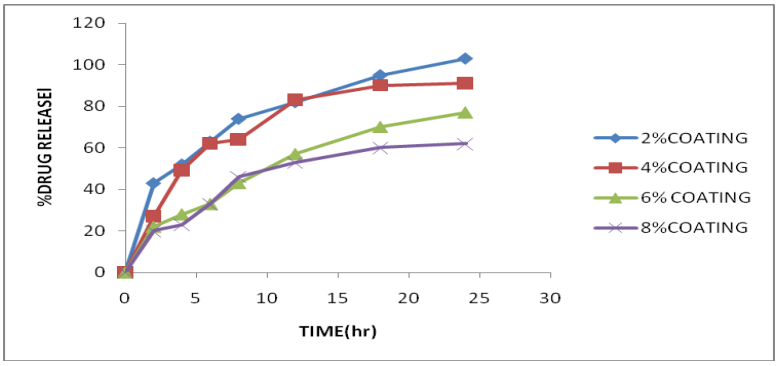

FIGURE 3 : Effect of Coating weight gain

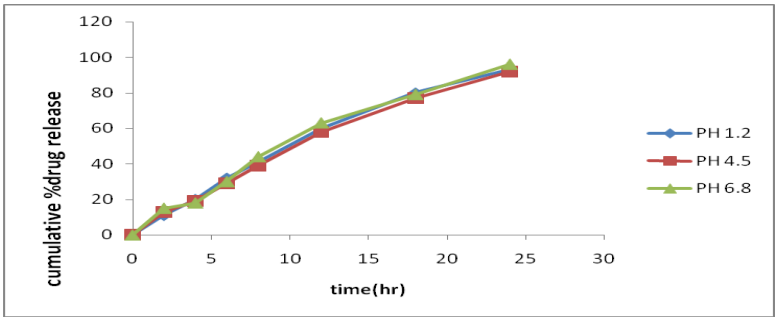

FIGURE 4 : Effect of PH concentration

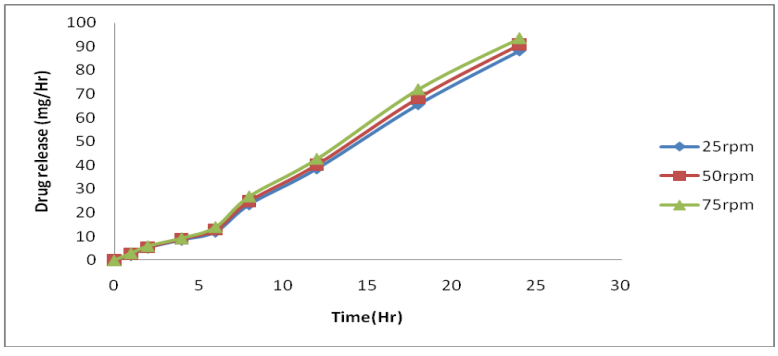

FIGURE 5 : Effect of Agitational intensity

REFERENCES

1. Sastry SV, DeGennaro MD, Reddy IK, Khan MA: Atenolol gastrointestinal therapeutic system. Part 1. Screening of formulation variables, Drug Dev. Ind. Pharm., 1997, 23 (2) pp.157–165.
2. Zentner GM, Rork GS, Himmelsteic KJ: Controlled porosity osmotic pump US Patent 4968,507, 1990.
3. Zondervan GJ, Hoppen HJ, Pennings AJ, Fritschy W., Wolters G, Van Schilfgaarde R: Design of a polyurethane membrane for the encapsulation of islets of Langerhans. Biomaterials, 1992; 13 pp.136–144.
4. Elchidana PA, Deshpande SG: Microporous membrane - drug delivery system for indomethacin. J. Controlled Release, 1999; 59:279–285.
5. Lin SY, Chen KS, Run-Chu L: Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer permanence of eudragit acrylic films. J. Control. Release, 2000; 68: 343–350.
6. Flosser A, Kolter K, Reich HB, Schepky G: Variation of composition of an enteric formulation based on Kollicoat MAE 30 D. Drug Devel. Ind. Pharm., 2000; 26(1): 177–187.
7. Okarter TU, Singla K. The effects of plasticizers on the release of metoprolol tartrate from granules coated with a polymethacrylate film. Drug Devel. Ind. Pharm., 2000;26(1) : 323– 329.
8. Anker M, Stading M, Hermansson AM: Effects of pH and the gel state on the mechanical properties, moisture contents, and glass transition temperatures of whey protein films. J. Agric. Food Chem., 1999;47 : 1878– 1886.
9. Appel LE Clair JH, Zentner GM: Formulation and optimization of a modified microporous cellulose acetate latex coating for osmotic pumps. Pharm. Res., 1992;9:1664–1667.
10. Sarisuta N, Saowakontha R, Ruangsuksriwong C: Effects of surfactant on release characteristics of clonidine hydrochloride from ethylcellulose film. Drug Devel. Ind. Pharm., 1999;25(2) :373– 377.
11. Repka MA, McGinity JW: Influence of vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion. Int. J. Pharm., 2000;202 pp. 63–70.
12. Hutchings J, Sakr DE: Influence of pH and plasticizers on drug release from Ethylcellulose pseudolatex coated pellets. J. Pharm. Sci., 1994;83: 1386– 1390.
13. Siepmann J, Lecomte F, Bodmeier R: Diffusion-controlled drug delivery systems. calculation of the required composition to achieve desired release profiles. J. Control. Release, 1999;60: pp.379– 389.
14. Santus G, Baker RW: Osmotic drug delivery: a review of the patent literature. J. Controlled Release,1995;35: 1–21.
15. McClelland GA, Sutton SC, Engle K, Zentner GM: The solubility-modulated osmotic pump: in vitro/in vivo release of diltiazem hydrochloride. Pharm. Res., 1991;8:88–92.
16. Verma RK, Mishra B, Garg S: Osmotically controlled oral drug delivery. Drug Dev. Ind. Pharm., 2000; pp. 695–708.
17. Verma RK, Krishna DM, Garg S: Formulation aspects in the development of osmotically controlled oral drug delivery systems. J. Control. Release, 2002;79 : 7–27.
18. Thombre AG, DeNoto AR, Gibbes DC: Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. J. Control. Release, 1999;60: 333–341.
19. Shireesh Kiran R, Chandra Shekar B, Nagendra Babu B, Swetha G, Nagamani D, Prasad MVV: Design and Characterization Of Sustain Release Intragastric Hydrodynamic Balanced Tablets of Propranolol Hydrochloride. Int J Nov Drug Deliv Tech. 2011; 1(1): 12-22.

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