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Research Article

MULTIPLE-UNIT CONTROLLED RELEASE PLATFORM FORMULATION BY WRUSTER PROCESS

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ABSTRACT

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy.

Objective: The present investigation was undertaken to fabricate modified release tablet of metoprolol succinate using multiple unite pellets systems with Wruster process.

Method: In the present study the effect of release modifier such xanthan gum, Carbomers, Eudragit, Kollidone SR, hydroxypropyl methylcellulose and Ethylcellulose was investigated. Drug loaded pellets was analysed using PXRD and FTIR spectroscopy. The in vitro drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The similarity factor (f2) was calculated for selection of best batch considering mean in vitro dissolution data of marketed formulation as a reference profile.

Conclusion: It is concluded that the desired drug release pattern can be obtained by using a proper combination of HPMC and ethylcellulose.

Keywords: Platform Technology; Wruster Process; Metoprolol Succinate; Release modifier; Pellets

INTRODUCTION

Now days Pharma companies are engaged in the development of multiple Platform Technologies for controlled release, liposomes, taste- masking, oral fast dispersing dosage forms and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon and transmucosal routes and delivery of macromolecules. The technologies behind oral drug delivery have emerged from the mainstream of Pharmaceutical industry and have become influential forces in their own right as evidenced by the burgeoning "drug delivery companies" that are at the forefront of innovation and hold their own niche market.[1]

Platform technology can work as a common base comprising of polymeric system with release modulator and able to accommodate the various drugs with common physicochemical / therapeutic properties with minimal changes. [2] A platform drug delivery system allows a company to use one drug delivery system for several drugs. This builds an internal base of experience, which can shorten development, and scale-up times, improve quality control, and better utilize manufacturing capabilities. The utility of system is directly related to its complexity [3]

Developing oral sustained release platform technology for freely water soluble drugs having strong first pass metabolism has always posed a challenge to the pharmaceutical technologist. Most of these highly water soluble drugs, if not formulated properly, are released at a high rate and are likely to produce toxic concentrations when administered orally.[4] Polymeric film coatings are often used for achieving sustained release of an active substance from pharmaceutical formulation because a coated dosage form enables prolonged and precise release of drug with good reproducibility.[5;6] One of the most widely used hydrophobic polymers in pharmaceutical film coating is ethyl cellulose due to its convenient film formability, good physiochemical properties and minimum toxicity.[7] Ethyl cellulose is a good polymer for modified release coating. The polymer is usually used in combination with a secondary polymer such as hydroxypropyl methylcellulose which confers the film a more hydrophilic nature and alters its structure by virtue of pores and channels through which the drug substance can diffuse more easily to control the release properties of a drug formulation.[8] Ethyl cellulose coating require plasticizer which is essential to enhance film forming characteristics, workability and serviceability.[9] Pellets as a drug delivery system offer not only technological advantages but also better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing. [10] It also has therapeutic advantages such as less irritation of the gastrointestinal tract, a low risk of side effects associated with dose dumping and reduction of the variation in gastric emptying rates. [11] Pellet coating is preferably performed by fluid bed technology due to homogeneous coating leading to an efficient and predictable drug release. In a fluidized bed coater, the particles are fluidized by air, while a liquid suspension is sprayed onto the particles. Four key processes are important for the coating process quality control particle-droplet impact and adherence, liquid spreading, drying and accidental particle agglomeration. [12]

The Wurster apparatus is most commonly used for the coating of small particles [13;14] A controlled fluidization of the primary particles is provided by process air forcing them to follow a circulation flow trajectory (Figure 1) producing homogeneous and very dense films. [15] Furthermore, there is only low risk of spray drying of the atomized droplets so that the process may run in a wide range of coating liquid viscosity, spray rate, process air volume and process air temperature. [16] An insert bottom spray granulator/coater with Wurster partition can be divided into four parts [16] the spouting zone (1) where particles are sucked by the process air to the entry of the Wurster partition.

Particles are wetted in this area by the sprayed coating liquid. In the upper part (2) of the Wurster partition the particles are transported by pneumatic conveying opposite to the gravitation force, and solvent evaporation and drying takes place. In the annular zone (3) the particles fall downward to the bottom of the process chamber and in the tampon zone (4) the particles are accelerated and sucked into the spouting zone. The filter housing with textile filters on the top of the apparatus prevents the particles from leaving the process chamber providing low material loss. To achieve an homogeneous coating, the wetted particles must be dried during the transit in the upper zone of the Wurster partition. Otherwise, if too wet particles reach the annular zone, they will stick and agglomerate because of the low velocity compared to that in the Wurster partition. [17]

Metoprolol succinate, a white crystalline powder, is freely soluble in water. Since the solubility of metoprolol succinate is lower at neutral pH, compared to acidic pH, it is released by the mechanism of diffusion through an insoluble polymer film.[18] It is a cardio selective β-blocker that has been classified as a class I substance according to the Biopharmaceutics Classification System, meaning that it is highly soluble and highly permeable.

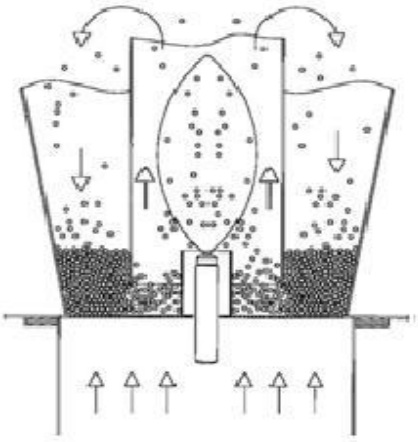

Fig. 1: Diagram of the Wurster process [15]

The drug is readily and completely absorbed throughout the intestinal tract [19] but is subjected to extensive first pass metabolism resulting in incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentration occurs after about 1 to 2 h. The drug is eliminated within 3 to 4 h which, depending on therapeutic activity, makes it necessary to administer the formulation up to 4 times daily. Based on these properties and well defined relationship between the beta blocking effect and plasma drug concentration, metoprolol lends itself to a sustained release formulation.

The goal of this study was to develop a controlled release platform technology multiparticulate dosage form as a tablet of metoprolol succinate to reduce the dosing frequency from three times to once a day, and to study the stability of these formulations. Sustained release platform technology multiparticulate tablets of metoprolol succinate were prepared by the compression technique in which sustained release pellets were mixed with the cushning agent like Perlitol SD 200, Prosolv HD90 and lubricant magnesium stearate.

MATERIAL AND METHODS

Materials

Non Pareil Spheres (M.B Sugars Ltd); Microcrystalline Cellulose Pellets (Spansules Formulation India); Metoprolol Succinate (Lupin Pharma); Povidone (PVP K 30) (BASF India) ; Eudragit NE 30D (Evonik India) ; Ethyl Cellulose (Dow Chemicals India); HPMC (Dow chemical's) ; Kollidone SR 30 D (BASF India); Polyethylene glycol (Vasudha Pharma; Talc; Microcrystalline cellulose PH 102; Pregelatinized starch; Dicalcium Phosphate (Sudip Pharma); Silicified microcrystalline cellulose (Prosolv HD 90) (JRS Pharma Company Germany); Stearic acid (Vasudha chemicals, India) ; Kollidone VA 64 (BASF India); Sodium stearyl fumarate (Vishwat Pharma); Magnesium Stearate (Sunshine organic).

Methods

Preparation of the Drug coat:

Metoprolol succinate was dissolved in aqueous solution of Polyvinyl Pyrrolidone with continuous stirring to form clear solution. [19]

Table 1: Fluid bed coating process parameters

Parameter	Set Values
Inlet Temperature	$60^0C \pm 5^0C$
Bed Temperature	42^0C
Outlet air Temperature	42^0C
Inlet air Pressure	1 to 2
Spraying nozzle Diameter	1.2 mm
Liquid Spray nozzle Pressure	1-3 bar
Filter Air purging Pressure	1-3bar
Peristaltic Pump RPM	1 to 2
Perforated plate	Type C
Partition diameter / length	74 / 250 mm
Distance partition-plate	1cm

Wruster coating

The coating process was performed in a laboratory fluid bed processor (UFBM-1/05Umang fluid bed Multiple 1 Umang Pharamtech, Germany) equipped with Wurster partition. Process parameters was set as mention in Table 1

Preparation of polymer dispersion

An organic dispersion of Ethyl cellulose and Hydroxypropyl methyl cellulose was prepared in isopropyl alcohol and methylene chloride. This mixture was stirred for 30min and to it adds plasticizer to form clear solution. The polymeric dispersion was passed through # 200 mesh nylon cloth.

Coating of drug pellets with polymer dispersion

In a mixture of dispersion of varying concentrations of Ethyl cellulose and HPMC E15. The mixture was stirred using a magnetic stirrer prior to and throughout the coating process. The drug pellets were coated at different coating loads by the solution layering technique. Coating parameters were set as shown in Table I. The coating fluid was sprayed onto the pellets with an intermittent drying time of 5 min

Preparation of MUPS tablets

MUPS tablets were prepared by the direct compression approach using the compositions shown in Table 2. Drug loaded pellets were mixed with microcrystalline cellulose, Prosolv HD 90 and Kollidone VA64 in a laboratory scale blender [octagonal Blender, Anchor Mark] for 10 min. Finally, magnesium stearate passed through a 250 µm sieve was added to the mixture and blended for 5 min. The degree of filling of the blending vessel was 50% by volume to ensure proper mixing. The tablets of 360 mg ± 5% were compressed using one set of 11 mm flat face beveled edge punch on a 12-station automated single rotary compression machine [Anchor mark]. The compression machine is equipped to measure the compression forces applied to the blend. Considering the criticality of the compression process, the machine speed was set to 10 rpm. Minimum gap was maintained between the turret and the feed frame to minimize the physical stress on the blend during rotation. Tablets were compressed at different compression forces in a 2-6 kg/cm2 range in order to obtain tablets with a crushing strength ranging from 0.3 to 1%

Characterization of pellets and compressed tablets

Characterization of pellets:

Flow Properties

Non pareil seeds were evaluated visually to check the spherical nature. The flow property of these was studied using the following tests:

Carr's index

Carr's index value for uncoated pellets and coated pellets were determined using formula [8]

$$Carr's\ Index\ (\%) = \frac{Tapped\ Desity - Bulk\ Desity}{Tapped\ Desity} \times 100$$

Angle of repose

The static angle of repose of uncoated pellets and coated pellets was measured by the fixed funnel and free-standing cone method [8] using the formula:

Angle of repose (θ) = $\tan^{-1} h/r$

Where: h-height of the heap; r-radius of the flat surface occupied by pellets

Determination of drug loading content and encapsulation efficiency

Accurately weighed quantities of pellets were dissolved in 100 ml of 0.1N HCL and filtered through membrane filter (0.45µ). The filtrate

was diluted and assayed by using spectrophotometer at 271 nm (JASCO V500, Japan). Entrapment efficiency was calculated by;

$$Entrapment\ Efficiency\ (\%) = \frac{Actual\ Drug\ content\ in\ pellets}{Theoratical\ Drug\ Content\ in\ pellets} \times 100$$

Powder X-Ray Diffractometry (PXRD)

The crystalline properties of pure metoprolol Succinate, placebo pellets and drug loaded pellets, were studied using X-ray diffractometer (PW 1729, Philips, Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed at 2θ between 5o to 50o. The voltage and current used were 30 kV and 30 mA respectively. The range and the chart speed were 2 × 103 CPS and 10 mm/degree 2θ, respectively.

FT-IR spectrophotometry

FT-IR analysis was performed on MS, HPMC and Ethyl cellulose in bulk, MS in a physical mixture with both ethyl cellulose and HPMC (1:1) and on the microparticles. An FT-IR spectrophotometer (Alpha-FT-IR, Bruker Optics, Germany) was used for recording the spectra of the samples in nujol mull.

Characterization of multiparticulate sustained release tablet

The evaluation parameters of multiparticulate tablet of tablet size, tablet thickness, weight variation, hardness, friability, drug content.

Scanning electron microscopy

The morphology of the surfaces and cross sections of the coated pellets were examined before and after compression by scanning electron microscopy (SEM).[20] The dried samples were coated by platinum coating using an auto fine coater (JEOL-JFC 1600, Japan) and then observed under different magnifications with an analytical scanning electron microscope (JEOL-JSM 6360A, Japan).

In-Vitro drug release

The *in-vitro* drug release study was carried out in a phosphate buffer of pH 6.8 at 37 ±0.5ºC, using USP I dissolution apparatus (Electrolab-model TDT-06L). A total amount of microparticles equivalent to 10 mg of drug was placed in the basket.

The basket was rotated at 50 rpm for 20 h. After pre-determined time intervals 1, 4, 8, and 20 h aliquots of 5 ml from the dissolution medium were withdrawn and the same volume of phosphate buffer pH 6.8 maintained at 37 ±0.5ºC were replaced immediately.

The samples were then analyzed by UV-Vis spectrophotometry (λmax = 274nm) and the amount of the released drug was calculated.

RESULTS AND DISCUSSION

Physical characteristics of pellets

Non pareil seeds and sustained release pellets having Carr's index value in the range 14-16% and angle of repose of 22-24^0 showed good flow property. [21] The details of results are shown on table 3

Determination of drug encapsulation efficiency

Amount of drug in pellets was found to be 90 to 95% estimated spectrophotometrically. The details of results are shown on table 3.

Table 3: Details of Flow properties and encapsulation efficiency

Parameters	CR1	CR2	CR3	CR4	CR5	CR6	CR7	CR8	CR9	CR10	CR11
CI (%)	15.89	16.86	12.99	12.93	12.44	12.54	13.93	14.92	15.35	16.00	15.91
AOR (^{0}C)	27.02	26.09	27.15	28.56	27.45	25.68	28.49	27.48	26.89	28.14	27.15
EE (%)	91.62	92.97	90.77	93.92	92.96	94.55	92.55	91.42	92.50	93.00	90.35

CI=Compressibility Index; APR = Angle of Repose; EE= encapsulation efficiency

Powder X-Ray Diffractometry (PXRD

The XRD pattern of MS, HPMC, ethyl cellulose individually and formulation pellets are shown in the Figure. The diffraction pattern of MS showed numerous characteristic peaks at 2θ = 13.85, 19.19, 22.44, 23.6, 25.59, 26.57 and 43.63º, which are not present in the formulation MP4. This is an indication that the drug dissolved in the carrier state carrier matrices in amorphous form rather than the original crystalline form. This was obvious because of the solubility of drug in water initially, and followed by encapsulation of it in the polymeric matrix as molecularly dispersed form. This indicates that drug was encapsulated within the polymer matrix effectively. Three peaks at 2θ = 38.41, 43.6 and 65º were present, (figure 2) which could be due to the presence of the polymer in microparticles.

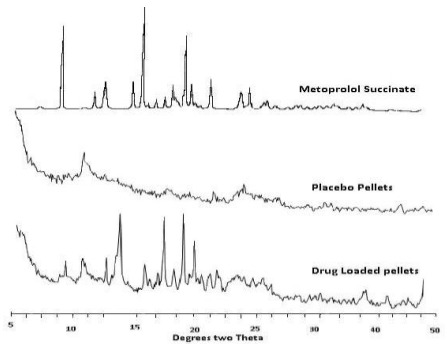

Fig. 2: PXRD graph Metoprolol Succinate, placebo pellets and Drug loaded pellets.

FT-IR spectrophotometer

FT-IR spectroscopy was carried out to investigate the possibility of interaction between MS and polymers. MS has the characteristic broad peaks at 3397.63 and 3148.66 cm-, attributable to its vibrational stretching of O-H and functional N-H bond, respectively. Other peaks are; C-O-C stretching vibration at 1114.24 cm–; C-N stretching at 1242.23 cm-; C = C aromatic stretching vibration at 1563.76 cm-; C-H streching at 2923.97 cm- and C-O streching at 1385.12 cm-. The used carriers have lots of O-H groups (both HPMC and ethyl cellulose) and C = O groups (ethyl cellulose) that may react with the above groups of MS. Such types of interactions result from the formation of hydrogen bonding between drug and polymers that will lead to frequency shifts or splitting in absorption peaks. As can be seen from the spectra (Figure 3) of physical mixture of MS and ethyl cellulose and microparticles, the peaks at 3148.66 cm– (functional peak for N-H bond) and 1611.18 cm– (C = O group) disappeared, indicating that there could be an interaction involved between C = O group of ethyl cellulose and N-H group of MS. In addition, there was no evidence of interaction in the spectra of physical mixture of drug and HPMC.

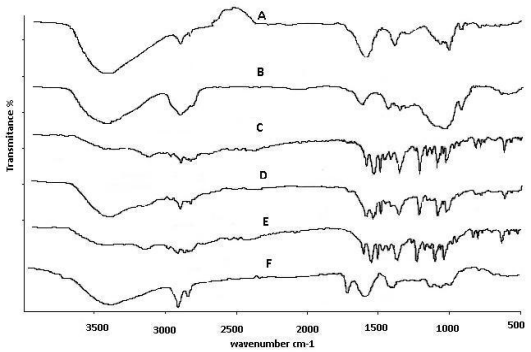

Fig. 3: FTIR of A= Ethyl cellulose; B=Hydroxypropyl methyl cellulose; C= Metoprolol Succinate; D=Metoprolol + Ethyl cellulose; E= Metoprolol Succinate + Hydroxypropyl methyl cellulose; F= Drug loaded Pellets

Table 4: Details of physical properties of MUPS tablet

Parameters	CR1	CR2	CR3	CR4	CR5	CR6	CR7	CR8	CR9	CR10	CR11
Thickness (mm)	3.84	3.86	3.84	3.87	3.80	3.76	3.80	3.90	3.84	3.86	3.84
Hardness (kg/cm²)	6.5	7.2	6.8	7.4	7.8	9.1	8.5	8.4	8.9	9.1	9.5
Friability (%)	0.45	0.58	0.58	0.57	0.59	0.78	0.71	0.69	0.24	0.19	0.16
Drug content (%)	99.62	95.97	96.77	98.92	99.96	97.55	99.55	98.42	99.50	99.00	98.35

Characterization of metoprolol Succinate multiparticulate tablet

The evaluation parameters of multiparticulate tablet of tablet size, tablet thickness, weight variation, hardness, friability, drug content were as depicted in Table 4

Scanning electron microscopy

The coatings of non pareil seeds (Figure 4A), coated pellets (Figure 4B), sustained release pellets after compression (Figure 4C) and cross-section of compressed MUPS tablets (Figure 4D) were studied by scanning electron microscopy at both low and high magnifications. The coated pellets at low magnification appeared as spherical discrete units and the surface morphology. The cross section of tablets shows the intact pellets which indicate and does not break upon compression which will not affect the dissolution performance of MUPS.

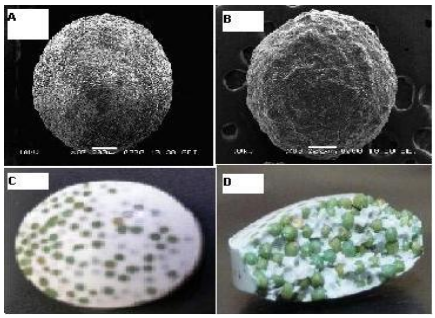

Fig. 4: Scanning electronic microscopy photos of A= non pareil seeds; B=coated pellets; C= MUPS tablets; D= cross-section of compressed MUPS tablets

IN-VITRO DRUG RELEASE

Effect of Xanthan Gum on drug release

Xanthan gum is a hydrophilic polymer and high molecular weight extracellular hetero- polysaccharide with cellulose like backbone. The primary structure of this naturally occurring polymer consists of 1,4 linked β-D-glucose residues, having a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached to alternate D glucose units of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain. It has been reported that xanthan gum is useful candidate for controlled release and provide zero order kinetics. Furthermore, xanthan gum can maintain constant drug plasma levels in vivo. [22]

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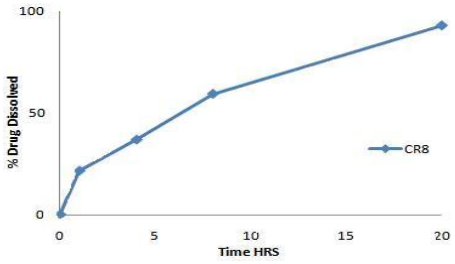

Fig. 5: Dissolution profile using the Xanthan Gum as release modifier

It has been reported that xanthan gum proved a better retarder to drug release than synthetic polymer. In the present study of batch No CR8 xanthan gum (Figure 5) was used in lubrication stage at 15 mg/tablets it was observed that the gum produce the gel mass at around the pellets and retarded the drug release. But overall the dissolution profile was matched with USP 36 monograph of metoprolol Succinate extended release tablets

Effect of Carbomers on drug release

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. In this investigation the polymeric materials used as retardant carriers. These synthetic, crosslinked, high molecular weight polymers are commercially available in various grades that differ from each other with respect to their molecular weight and architecture. Contact with water causes the polymers to hydrate, absorb water and swell fast. Their properties make them ideal for direct compression processes [23] and many are currently being used for controlling drug release in various pharmaceutical solid dosage forms. [24-26] lightly crosslinked polymers, such as Carbopol® 971P NF polymer, tend to be more efficient in controlling drug release than highly crosslinked polymers such as Carbopol® 974P NF polymer.

In this investigation used Carbomers show least release effect may due to behavior attributed to the different degree of cross linking density among the polymers used in this study. As mentioned earlier, C971 is the least cross linked polymer and consequently is less porous and has fewer channels, C934 is an intermediate, where as C974 exhibits the most cross links and has the most pores and channels [23]. The channels facilitate liquid penetration and the drug release in a tablet. Therefore, the polymer with more channels, C974, (Figure 6) demonstrated the highest release; quite the opposite C971, with fewer channels displayed the lowest release.

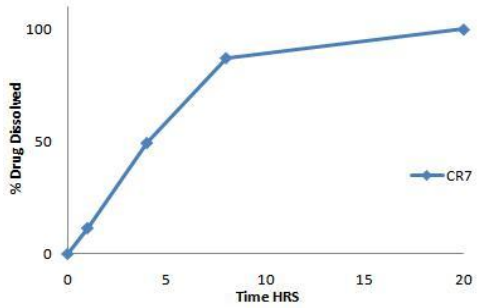

Fig. 6: Dissolution profile using the Carbomers 971P as release modifier

Effect of Kollidon SR on drug release

Kollidon SR is a relatively new matrix retarding agent consisting of 80% polyvinyl acetate and 20% polyvinylpyrrolidone. With its excellent flowability, this formulated combination allows sustained release dosage forms to be manufactured by the simple direct compression process. Kollidon SR is made by spray drying of the mixture of polyvinylacetate (PVAc) and polyvinylpyrrolidone (PVP) (PVAc: PVP = 4:1). The polyvinylpyrrolidone component gradually leaches out of the matrix during dissolution thereby creating the pores for the active to diffuse out. (Figure 7) The compressed polyvinyl acetate component maintains tablet core structure during dissolution. [27]

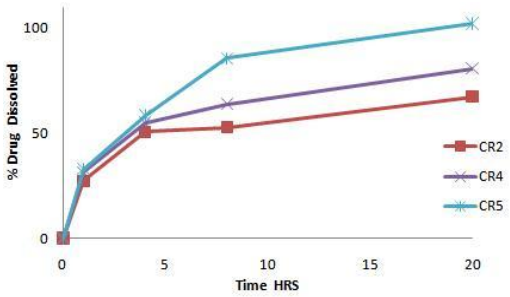

Fig. 7: Dissolution profile using the Kollidon SR as release modifier

Effect of Eudragit NE 30 D on drug release

Eudragit NE 30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate widely used to obtain reservoir type extended release formulation. It is insoluble but it can swell in water and has low permeability. [28] A water soluble additive may be included in the film to increase the permeability of the membrane when the product is exposed to an aqueous environment during the dissolution phase. [29, 30] The addition of a water- soluble additive may improve the reproducibility of release rate properties and compensate for variability in processing conditions. [31, 32] For these reasons an easy soluble polymer (low viscosity HPMC –Methocel E5 LV) was used as pore generating excipient. A three –factor, three-level full experimental design was applied to construct a second-order polynomial model describing the effect of the formulation factors on the characteristics of the product.

The amount of HPMC has the most important effect on the metoprolol release at all dissolution time points. The increase of the amount of HPMC increases the release of metoprolol tartrate for all dissolution time points (Figure 8).

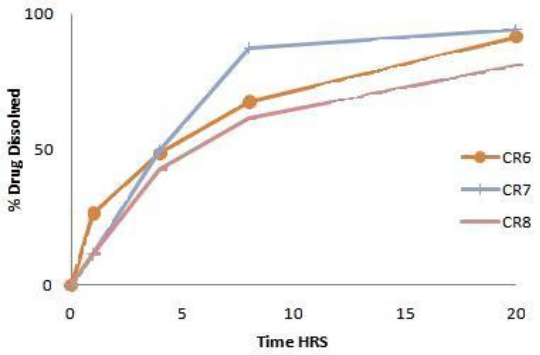

Fig. 8: Dissolution profile using the Eudragit NE30D as release modifier

Effect of HPMC and EC on drug release:

HPMC has been extensively used as a rate controlling polymer in oral ER dosage forms because its non-toxic nature, availability in different chemical substitution forms, high hydration rates and different viscosity grades. Rapid formation of a viscous gel layer upon hydration and the viscosity of the gel layer of HPMC govern its performance in an ER matrix system. [33] Upon formation of the gel layer, viscosity of the gel layer regulates the overall rate of drug release. In addition, variations in HPMC concentration from low to high (10–50%), results in broad differences in dissolution profiles. [34]

Cellulose ethers, especially hydroxypropyl methylcellulose (HPMC), are frequently used as the basis for sustained release hydrophilic matrix tablets. Despite studies in the 1960s describing their uses [35; 36], their characterization and performance have been more extensively quantified only recently. Their properties as gelling agents are very important in the formulation because they are responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer which is able to control drug release. [37] On the other hand, hydrophobic materials have also been employed as matrix carriers for sustained release solid dosage forms. [38, 39]

Ethyl cellulose (EC) is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. The properties of ethyl cellulose sustained release products, including film coated tablets,[40] microspheres, [41,42] microcapsules, [43] and matrix tablets for both soluble and poorly soluble drugs [44] have been reported. The combination of ethyl cellulose and a hydrophilic component such as HPMC offers a flexible system to tailor the drug release by changing the viscosity, substitution type and concentration of HPMC. [45] In general, designing controlled release drug delivery systems for providing 12 or 24 h zero order release kinetics, especially for highly water-soluble agents, is often difficult and unsuccessful.

This shortfall in delivery system design may be attributed to three factors:

(a) the high water solubility of the drug results in a burst effect;

(b) the lack of proper control over time-dependent processes of polymer relaxation and disentanglement in relation to drug dissolution and diffusion; and

(c) Compensation for increase in the diffusional path length with time is not easily achievable [46]

For drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix, for developing sustained release dosage forms.

Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications.

The presence of a highly water-soluble compound, fluorescine, in a HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and a large increase in gel thickness. In the presence of a solvent, the mobility of the polymer chains is enhanced, resulting in a gradual transformation of a glassy matrix to a rubbery swollen gel. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug. [47] Wan et al have also reported that other factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling. [48]

Incorporation of varying concentrations of ethyl cellulose (CR9, CR10 and CR11) controlled drug release. (Figure 9) This may be attributed to decreased penetration of the solvent molecules in the presence of the hydrophobic polymer, leading to reduced diffusion of the drug from the matrix. According to penetration theory, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. [49]

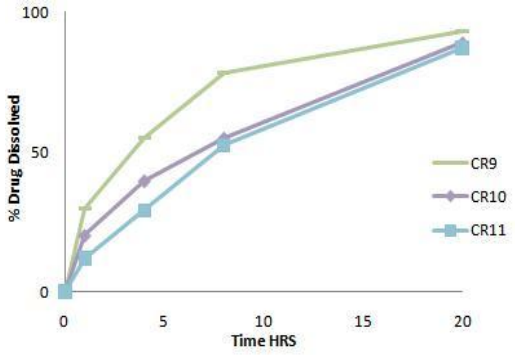

Fig. 9: Dissolution profile using HPMC and Ethylcellulose

Comparative dissolution profile of optimized formulation and marketed formulation

From data obtained by the feasibility search method, the formulation batch of HPMC and EC cellulose was selected for further study. The dissolution profile of the optimized formulation of sustained release pellets was compared with the marketed matrix tablet formulation as shown in Figure 10.Where as kinetics parameters studied are shown in Table 5 and found to be 84.29%

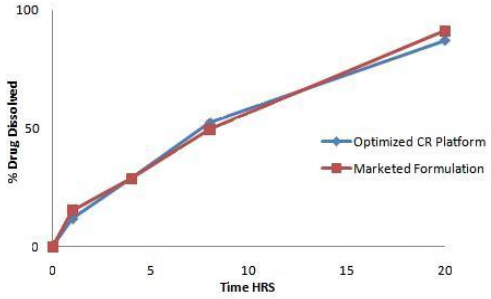

Fig.10: Comparative study of Dissolution profile of optimized formulation and marketed formulation.

Table 5: Kinetic models showing drug release pattern of formulated and marketed formulation

Formulation	Best fit Model	R^2	% Cumulative Release	$t_{50\%}$	$t_{80\%}$
Optimized platform	Zero order kinetics	0.9988	92.86±0.78	7.45±0.25	14.59±0.58
Marketed formulation	Higuchi	0.9991	94.15±0.28	8.0±0.56	15.50±0.64

CONCLUSION

Inert pellets of microcrystalline cellulose were successful coated with different amounts of the polymer coating. Polyvinylpyrrolidone and talc were added to the coating solution to increase layer stability and to prevent pellet agglomeration, respectively. The fluid bed coating processes were stable and reproducible. The yield was in the range 80-95% without any tendency due to increasing process time with lots of higher ratio coating to core.

The findings of the present study demonstrate that the developed controlled release platform with HPMC and EC could slow down the release profile of Metoprolol Succinate from their matrices. Incorporation of EC in HPMC matrix tablets was found to control drug release. Release kinetics analysis showed that drug release from formulations was adequately described by zero-order equation compared with marketed formulation. This approach for development of platform will be suitable for controlled delivery of highly soluble drugs such as metoprolol Succinate and other Class I drug.

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CONFLICT OF INTEREST

Author does not have any conflict of interest

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