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Formulation and Evaluation of Kollidon® SR for PH-Independent Extended Release Matrix Systems for Propranolol Hydrochloride

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Abstract

The characteristics of a new Polyvinylacetate/Povidone based excipient, Kollidon® SR were evaluated for application in extended release matrix tablets. The effects of the following formulation and process variables on tablet properties and drug release were tested: Kollidon® SR concentration in the tablet, addition of external binder for wet granulation, presence of an enteric polymer in the matrix, method of manufacturing and compression force. The similarities in release profiles were evaluated by applying the model independent f2 similarity factor. It was found that Kollidon® SR is suitable for pH-independent extended release matrix tablets. A minimum concentration of 30% polymer was necessary to achieve a coherent matrix, able to extend the release of the incorporated drugs. Increasing the Kollidon® SR concentration in the tablet led to a slower drug release. Drug release followed square root of time dependent kinetics, thus indicating a diffusion-controlled release mechanism. The drug release was influenced by the aqueous solubility of the drug. The drug release rate was faster for wet granulation than direct compression, thus making direct compression the method of choice for manufacturing Kollidon® SR extended release systems. It was found that Kollidon® SR was the main release controlling agent in the presence of an external binder or enteric polymer in the matrix. A significant reduction in the dissolution rates associated with an increase in tablet hardness was observed during the stability test under accelerated conditions. The developed propranolol matrix tablets formulation was compared to the reference listed product (Inderal® LA capsules). It was concluded that Kollidon® SR is a potentially useful excipient for the production of pH-independent extended release matrix tablets.

Keywords: Propranolol HCl, pH-independent release, Kollidon® SR, matrix tablet.

1. INTRODUCTION

The high cost involved in the development of new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery systems [1]. Oral administration of drug to patients at a controlled release rate; preferably at a constant linear release rate is advantageous in various clinical applications [2]. Many drugs (e.g. weakly acidic and basic drugs) demonstrate pH dependent solubility in the pH range of the gastrointestinal tract. The rate at which a drug goes into the solution when it is dissolved in a medium is proportional to the solubility of the drug in medium. Hence, pH dependent solubility in the pH range of the gastrointestinal tract lead to different dissolution rates in the different parts of the gastrointestinal tract. pH dependent drug release from controlled release dosage form drugs (e.g. weakly acidic and basic drugs) demonstrate pH dependent solubility in the pH range of the gastrointestinal tract. The rate at which a drug goes into the solution when it is dissolved in a medium is proportional to the solubility of the drug in medium. Hence, pH dependent solubility in the pH range of the gastrointestinal tract lead to different dissolution rates in the different parts of the gastrointestinal tract. Kollidon® SR was introduced to the pharmaceutical market recently, and thus its evaluation constitutes a novel research topic for the pharmaceutical industry. Polyvinylacetate/Povidone based polymer (Kollidon® SR) is a relatively new extended release matrix excipient. It consists of 80% Polyvinylacetate and 19% Povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica. Propranolol HCl was selected as a model drug here for the development of pH-independent extended release tablets.

2. MATERIALS AND METHODS

2.1 Materials

Propranolol HCl was obtained as gift sample from Dr. Reddy's Labs, Hyderabad, India. Ammonio methacrylate copolymer type B NF Eudragit® RSPO was obtained as gift sample from Rohm, Darmstadt, Germany. Polyvinyl acetate and Povidone based excipient, Kollidon® SR were obtained as gift samples from BASF, Ludwigshafen, Germany Other ingredients were purchased from S.D. Fine

Chem Ltd, Mumbai. Double distilled water was prepared in laboratory using all glass distillation apparatus. All materials used in the study were of analytical grade.

2.2 Methods

2.2.1 Tablet manufacture

Tablets were manufactured by direct compression or wet granulation, according to the process flow as presented in the Figure 1 and 2 respectively. In this study first the suitability of Kollidon® SR was evaluated for low-dose drug extended release systems, using propranolol HCl (10mg) as a model drug. A full factorial design was applied to study the effect of polymer concentration (10-50% w/w of the tablet weight) and the method of manufacture (direct compression and wet granulation) on tablet properties and drug release. Tablets were manufactured by direct compression or wet granulation method to a target weight of 133.33mg/tablet and hardness of about 10 KP, using 7 mm round punches.. For the wet granulation technology, the effect of the addition of an external hydrophilic or hydrophobic binder was investigated. Later Kollidon® SR was replaced in direct compression with a polymethacrylate polymer, Eudragit® RSPO at 30, 40 and 50% concentration levels and tablets were also prepared. To evaluate the potential of Kollidon® SR as matrix former for propranolol 80mg tablets (high dose), knowing that the development of monolithic extended release matrices for high dose highly soluble drugs presents a challenge manufacture of propranolol 80mg tablets with 40-60% Kollidon® SR with a full factorial for two factors at three levels each: polymer concentration (40, 50 and 60%) and compression force (1000, 2000, 3000lbs) were prepared. Here, 80 mg propranolol tablets were manufactured by direct compression according to the process flow chart using bisect capsule shaped punches (0.185 x 0.0.426 in) to a target weight of 225mg/tablet. Propranolol 80mg tablets were also formulated by increasing the polymer level up to 70% of the tablet weight and/or partial replacement of Kollidon® SR with of an enteric polymer (Eudragit® L100-55). The objective was to study the effect of addition of an enteric polymer on drug release and to modify the release to be close / similar to the USP requirements for extended release propranolol capsules. Tablets were manufactured by direct compression, using bisect capsule shaped punches (0.220 x 0.500 in) to a target weight of 275.86mg (~276mg) and hardness 10-15 kP.

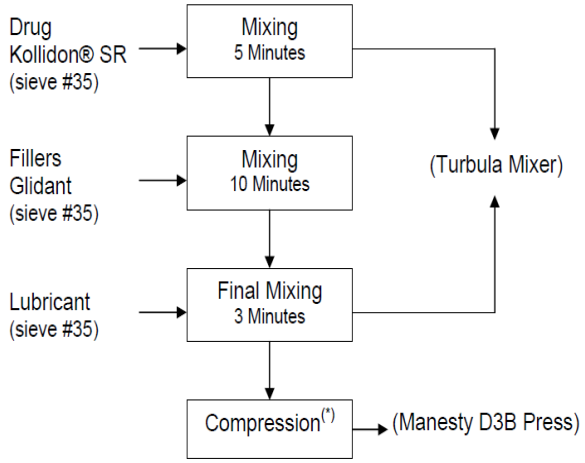

Figure 1: Process flow chart for tablets manufactured by direct compression

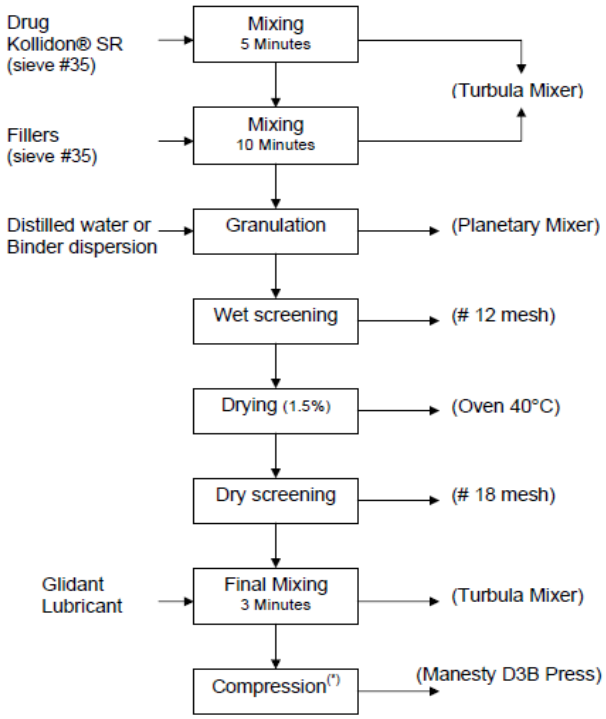

Figure.2: Process flow chart for tablets manufactured by wet granulation

Table: 1 Formulation of 10mg Propranolol tablets

Ingredients	*Formulations*											
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*
Propranolol HCl	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Kollidon®SR	10.00	20.00	30.00	40.00	50.00	30.00	30.00	50.00	50.00	-	-	-
Kollidon®30	-	-	-	-	-	5.00	-	5.00	-	-	-	-
Kollidone®SR30D	-	-	-	-	-	-	5.00	-	5.00	-	-	-
Eudragit® RSPO	-	-	-	-	-	-	-	-	-	30.00	40.00	50.00
Emcocel®90M	40.75	35.75	30.75	25.75	20.75	28.25	28.25	18.25	18.25	30.75	25.75	20.75
Emcompress®	40.75	35.75	30.75	25.75	20.75	28.25	28.25	18.25	18.25	30.75	25.75	20.75
Aerosol®200	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50

Table: 2 Formulation of Propranolol 80mg tablets

Ingredients (%)	*Propranolol 80mg tablets with 40-60% kollidone® SR*			*Propranolol 80mg tablets with 70% polymer*		
	40% KSR	*50% KSR*	*60% KSR*	*70% KSR*	*65% KSR + 5%Eudragit ®L100-55*	*60%KSR + 10%Eudragit ®L100-55*
Propranolol HCl	35.55	35.55	35.55	29.00	29.00	29.00
Kollidon® SR	40.00	50.00	60.00	70.00	65.00	60.00
Emcocel® 90M	11.725	6.725	1.725	-	-	-
Emcompress®	11.725	6.725	1.725	-	-	-
Eudragit® L100-55	-	-	-	-	5.00	10.00
Aerosol® 200	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium stearate	0.50	0.50	0.50	0.50	0.50	0.50

Table3: Stability study design

Study	*Storage condition*	*Frequency of testing*	*Test preformed*
Long- term	25±2°C/ 60±5%RH	0, 1, 3, 6, 9 months	Appearance, weight, thickness, hardness, drug release – method B
Accelerated	40±2°C/75±5%RH	0, 3 and 6 months (9months included, although not required by ICH)	Appearance, weight, thickness, hardness, drug release – method B

2.2.2 In Vitro Drug Release

In vitro drug release was performed for the manufactured tablets according to the USP 25 "Dissolution procedure" <711>, over a 24-hour period, using an automated dissolution system. ***Method A*** - Apparatus 2 (paddle) was used at 50rpm, with 1000ml dissolution medium at 37°C; the UV absorbance of the dissolution medium was measured at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours. The release was calculated using a standard solution. The drug release was tested in different dissolution media: distilled water, 0.1N HCl and USP 25 pH=6.8 phosphate buffer. The pH range (pH = 1.2 – 6.8) was chosen to reflect the physiologic conditions of the gastrointestinal tract.

Method B - in addition to the general method (method A), some of the propranolol 80mg tablet batches were tested according to the USP dissolution method required in the propranolol 80mg extended release capsules USP monograph (apparatus 1, 100rpm, 900ml, first 1.5 hours pH 1.2 buffer, then pH 6.8 buffer). Additional sampling times (1.5 and 14 hours) were included in establishing the dissolution profile.

2.2.3 Comparison of Dissolution Profiles

The dissolution profile comparison may be carried out using model independent or model dependent method. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles.

$$f_1 = \frac{S_{t=1}^{n}(R_t - T_t)}{S_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 \times \log \{[1+(1/n) S_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\}$$

where, R_t and T_t represent the average percent dissolved at time t for reference and test, respectively, and n is the number of time points tested. Dissolution profile was considered satisfactory if f_1 values lies below 15 (nearing zero) and f_2 value lies more than 50 (nearing 100).

2.2.4 Testing of propranolol 10mg tablets

Tablets were tested for physical properties and in vitro drug release according to the USP 25 (apparatus 2) paddle method at 50 rpm in 1000 ml of distilled water maintained at 37±0.5°C. The effect of dissolution medium on drug release was tested for the formulations with 30, 40 and 50% Kollidon® SR. The release profiles in three different dissolution media, distilled water, USP pH 6.8 phosphate buffer and 0.1N Hydrochloric acid were compared using the FDA recommended approach (f2 similarity factor). The applicability of the diffusional release mechanism (Higuchi time square model) was assessed.

2.2.5 Testing of propranolol 80mg tablets with 40-60% Kollidon® SR

Tablets were tested for physical properties and drug release in distilled water, 0.1N HCl and pH 6.8 buffers. The released amounts were plotted as function of square root of time, to determine the mechanism of drug release. A model independent approach using similarity factor f2 was used to compare the dissolution profiles.

2.2.6 *Testing of propranolol 80mg tablets with 70% polymer (Kollidon® SR alone or in combination with Eudragit® L100-55)*

Tablets were tested for physical properties and drug release in various media (method A) and according to the USP method for propranolol extended release capsules (method B). The release data obtained were plotted as a function of square root of time, to determine the mechanism of drug release. A model independent approach using similarity factor f2 was used to compare the dissolution profiles.

2.2.7 Testing of Inderal® LA capsules (reference listed drug product)

Inderal® LA (lot #9010268), the reference listed product, was tested for the drug release in different media according to method A and method B. This step was necessary because the reference listed product served as comparison for some of the developed matrix tablet formulations.

2.2.8 Effect of storage on tablet physical properties and drug release

Propranolol 80mg tablets with 65% Kollidon® SR were stored in HDPE bottles in the presence of desiccant under different storage conditions (FDA, 2001 ICH Q1A, FDA, 1997 ICH Q1C). At predetermined time points, the tablets were sampled and tested for physical properties and drug release.

TABLE- 4 (A) Effect of Kollidon® SR on physical properties of propranolol 10mg tablets manufactured by direct compression

Kollidon®SR	*Weight (mg)*		*Thickness (mm)*		*Hardness (kP)*	
	Average	*RSD*	*Average*	*RSD*	*Average*	*RSD*
10%	131.49	0.577	3.897	0.172	4.14	14.324
20%	132.75	0.725	3.923	0.173	6.47	7.252
30%	132.78	0.001	4.007	0.407	8.91	11.524
40%	133.87	1.264	4.152	1.077	11.54	10.024
50%	133.68	0.001	4.224	0.488	13.12	10.300

TABLE-4 (B) Effect of Kollidon® SR on the physical properties of Propranolol 10mg tablets manufactured by wet granulation

Kollidon® SR	*Weight (mg)*		*Thickness (mm)*		*Hardness (kP)*	
	Average	*RSD*	*Average*	*RSD*	*Average*	*RSD*
10%	135.96	1.065	3.998	0.105	8.37	4.141
20%	134.84	1.419	4.029	0.273	9.4	6.784
30%	134.80	0.001	4.079	0.270	11.11	8.055
40%	135.49	1.570	4.133	0.511	12.81	11.709
50%	133.3	0.002	4.207	0.663	11.40	7.725

Table 5: f2 values - effect of dissolution medium on drug release from propranolol 10mg tablets.

Formulation	*F2(0.1NHCl – water)*	*F2(pH 6.8 buffer-water)*
30% Kollidon ® SR direct compression	86.62	82.81
30% Kollidon® SR wet granulation	72.99	53.77
40% Kollidon® SR direct compression	94.30	72.33
40% Kollidon ® SR wet granulation	82.06	55.45
50% Kollidon ® SR direct compression	72.10	88.77
50% Kollidon ® SR wet granulation	75.44	84.31

Table 6: Effect of compression force and Kollidon® SR concentration on physical properties of propranolol 80mg tablets.

Compression force	*Weight(mg)*		*Thickness (mm)*		*Hardness (kP)*	
	Average	*RSD*	*Average*	*RSD*	*Average*	*RSD*
40% KSR						
1000lbs	222.62	0.800	5.075	0.104	5.79	8.824
2000lbs	223.4	0.534	4.761	0.459	10.62	4.587
3000lbs	223.92	0.797	4.576	0.537	16.80	5.383
50% KSR						
1000lbs	222.77	0.325	5.339	0.399	6.12	8.035
2000lbs	223.08	0.905	4.820	0.366	16.28	5.005
3000lbs	223.02	0.726	4.722	0.676	20.12	4.036
60% KSR						
1000lbs	224.07	1.196	5.616	0.1725.53	5.53	11.690
2000lbs	224.62	1.198	4.941	0.544	18.90	5.918
3000lbs	222.97	0.842	4.873	0.774	21.27	5.323

Table 7: Composition of the propranolol 80mg tablets formulation (65% Kollidon® SR).

Ingredient	*Manufacturer/lot*	*Amount (mg)/tablet*	*Percent/tablet*
Propranolol HCL (BP)	BASF C20011001	80.00	29.0
Kollidon®	BASF16-9006	179.309	65.0
Emcompress®	Penwest A20E	6.8965	2.5
Aerosil® 200	Dguessa D 10221D	1.3793	0.5
Magnesium Stearate	Manlinckrodt C19408	1.3793	0.5
	Total	**275.86**	**100.00**

3. RESULTS AND DISCUSSION

3.1 Propranolol 10 mg tablets

3.1.1 Effect of Kollidon® SR on drug release from propranolol 10mg tablets manufactured by direct compression

Propranolol 10mg tablets were manufactured with different concentrations of Kollidon® SR, (10, 20, 30, 40 and 50% of tablet weight). Tablets were uniform in weight and thickness and their hardness increased as the concentration of polymer in the formulation increased. It was found that increasing polymer concentration up to 40%, significantly decreased the drug release rate in water, sustaining the release of the highly water soluble drug incorporated at low dose for a longer period of time (dissolution data for all the experimental batches were reproducible n=6, RSD<3% and hence only the average values were plotted). There was no significant difference between the formulations containing 40% and 50% of the polymer content f2>50. The regression parameters of the drug release curves for formulations with 30- 50% polymer content are indicated in the plot of percent drug released versus square root of time is illustrated in Figure 4.

The high correlation coefficient (above 0.99) obtained indicates a square root of time dependent release kinetics. Thus, as the data

fitted the Higuchi model, it confirmed a diffusion drug release mechanism. It is suggested that the main driving force for the drug release in case of water soluble drug like propranolol hydrochloride from the matrix tablets is the infiltration of release medium. As the tablet is introduced into the medium, water penetrates into the matrix and povidone leaches out to form pores through which the drug may diffuse out. Also, as observed in, as the polymer level in the formulation is increased, drug diffusion is slowed due to the lower porosity and higher tortuosity of the matrix. Thus polyvinylacetate, which is a very plastic material, produces a coherent matrix, sustaining the drug release from the tablet matrix.

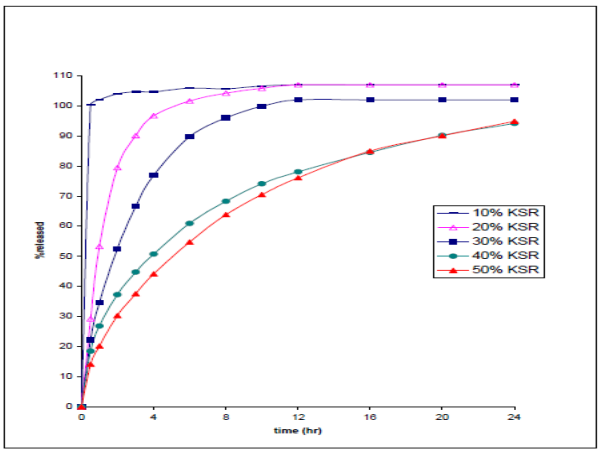

Figure 3: Effect of Kollidon® SR on drug release in water from propranolol 10mg tablets manufactured by direct compression.

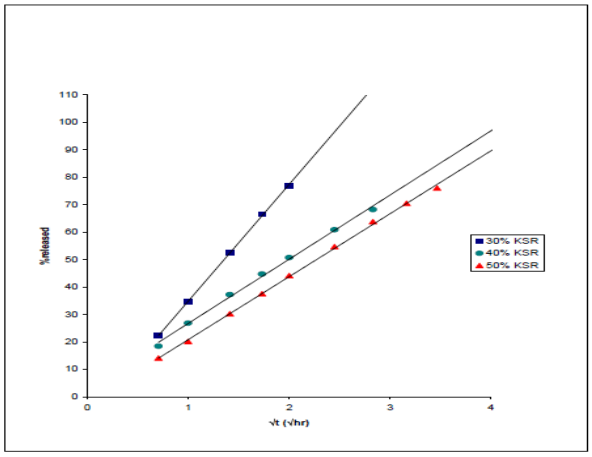

Figure 4: Effect of Kollidon® SR on diffusion controlled drug release in water from propranolol 10mg tablets manufactured by direct compression

3.1.2 Effect of Kollidon® SR on drug release from propranolol 10mg tablets manufactured by wet granulation.

The application of Kollidon® SR for tablets manufactured by wet granulation using distilled water as granulating medium was studied. Tablets were uniform in weight, thickness and hardness. The drug release in water is shown in Figure 5 and the Higuchi plots in Figure 6. By comparing the slopes of Higuchi plots as an indicator for release rate, it can be seen that wet granulation produced a faster release than direct compression. In contrast to the direct compression method, in tablets manufactured by wet granulation, increasing the polymer concentration from 30 to 50%, produced a faster rate of drug release from the matrix.

The regression parameters for Higuchi model and the change in release profiles is indicated by the varying slope values for the square root of time plots. This behavior could be attributed to a faster penetration of waterfront into the matrix, leading to a formation of more porous structure in the matrix. The povidone in the polymer would have deposited on the polyvinylacetate particles during granulation, thus localizing as discrete granules between polyvinylacetate particles, leading to a faster channeling action. The lower tortuosity and higher water penetration due to an increase in the volume of povidone at 50% polymer content, could also lead to a faster drug release rate.

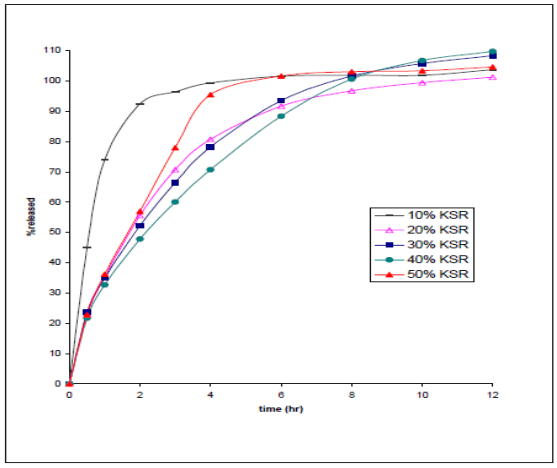

Figure 5: Effect of Kollidon® SR on drug release in water from propranolol 10mg tablets manufactured by wet granulation.

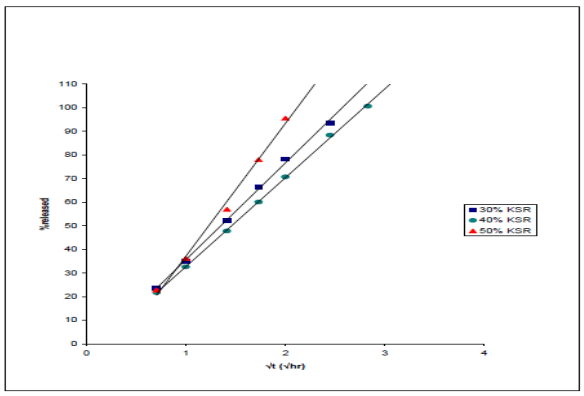

Figure 6: Effect of Kollidon® SR on diffusion controlled drug release in water from propranolol 10mg tablets manufactured by wet granulation

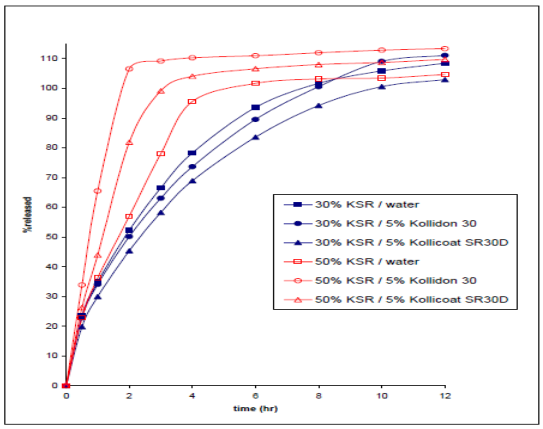

Figure 7: Effect of external binder on drug release in water from propranolol 10mg tablets with 30% and 50% Kollidon® SR

3.1.3 Effect of external binder on drug release from propranolol 10mg tablets manufactured by wet granulation

The effect of the addition of an external binder in the granulating medium, on the drug release rate from formulations containing 30 and 50% Kollidon® SR content was evaluated and the release profiles are as shown in Figure 7. The two binders studied at 5% concentration levels were water-soluble Kollidon® 30 and Kollicoat® SR30D aqueous dispersion with hydrophobic properties. No significant change in drug release profiles (f2 >50) was observed at 30% Kollidon® SR level. At a concentration of 50% Kollidon® SR, additional external binder did not slow the release as expected. None of the two binders used could compensate for the reduced interaction of the hydrophobic polyvinylacetate with the other hydrophilic components from the tablets. The results indicated that Kollidon® SR was primarily controlling the drug release rate.

3.1.4 Effect of dissolution medium on drug release from propranolol 10mg matrix tablets

Drug release from tablets with 30, 40 and 50% Kollidon® SR was tested in three different dissolution media: distilled water, USP pH 6.8 phosphate buffer and 0.1N hydrochloric acid. On applying the similarity factor, f2, to compare the dissolution in 0.1N HCl or pH 6.8 buffer to the release in water, values of above 50 were obtained indicating the similarity of the release profiles. Kollidon® SR contains no ionic groups, hence it is inert to drug substances and its solubility and hydration are not influenced by pH. As a result, the drug release was pH-independent and it was concluded that Kollidon® SR is suitable for the manufacturing of pH-independent extended release matrix tablets, on the condition that drug solubility does not drastically change with the pH.

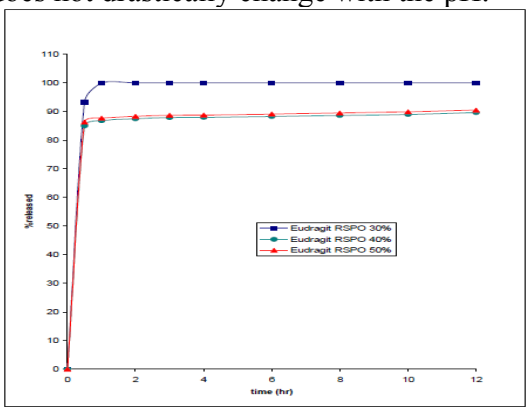

Figure 8: Effect of Eudragit® RSPO on drug release in water from propranolol 10mg tablets

3.1.5 Drug release profiles from matrix tablets with Eudragit® RSPO

Kollidon® SR was replaced in direct compression with a polymethacrylate polymer, Eudragit® RSPO. Tablets with 30, 40 and 50% polymer levels were manufactured and the drug release profiles in distilled water were compared. The drug release was faster, with about 80-100% of propranolol released in the

first 1-2 hours, which was attributed to a rapid and complete erosion of the matrix (disintegration time for all Eudragit® RSPO formulations tested was less that 10 minutes). This was a result of a low cohesiveness of the powder during compression, the maximum hardness which could be achieved (under maximum compression force) was between 4-6kP.

3.2 Propranolol 80mg tablets

3.2.1. Effect of Kollidon® SR and compression force on physical properties and drug release from propranolol 80mg tablets.

Previous results suggested a minimum Kollidon® SR concentration of 30% is necessary for a coherent matrix, able to extend the drug release. Considering this previous finding and the higher drug dose to be used (80mg) the minimum concentration of Kollidon® SR for this set of experiments was 40%. Tablet formulations with 80mg propranolol and 40-60% Kollidon® SR were evaluated with regard to the robustness of the release to variations in compression forces, which may occur during manufacturing. The resultant tablets were uniform in weight, thickness and hardness, as shown in Table 6. For tablet formulations containing 40-60% Kollidon® SR, it was observed that while changes in the compression forces from 1000 to 2000 lbs produced an increase in tablet hardness and a slight decrease in dissolution rate (not significant according to the f2 similarity factor, further increase to 3000 lbs did not affect the drug release profiles.

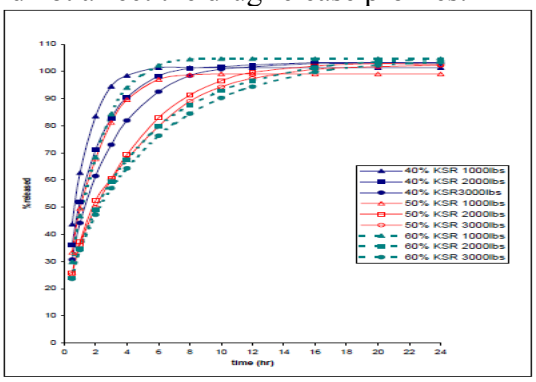

Figure 9: Effect of Kollidon® SR and compression force on drug release in water from propranolol 80mg tablets.

Therefore a robust delivery system was attained at compression force above 2000 lbs and this represented a definite advantage of these formulations. Increasing the Kollidon® SR concentration in the tablet led to an increase in tablet hardness, as shown in Figure. Release profiles of the tablets that were formulated with 40-60% Kollidon® SR and compressed under 2000 lbs.

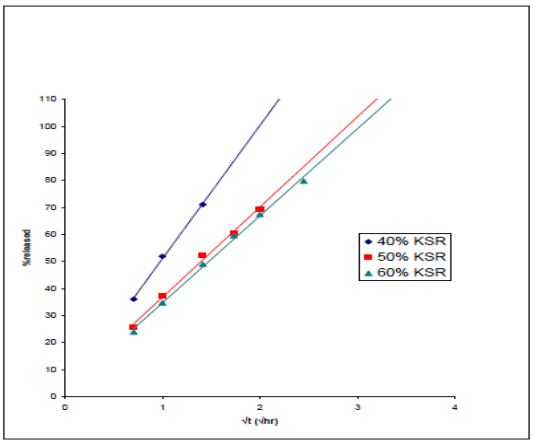

Figure 10: Effect of Kollidon® SR on diffusion controlled drug release from propranolol 80mg tablets.

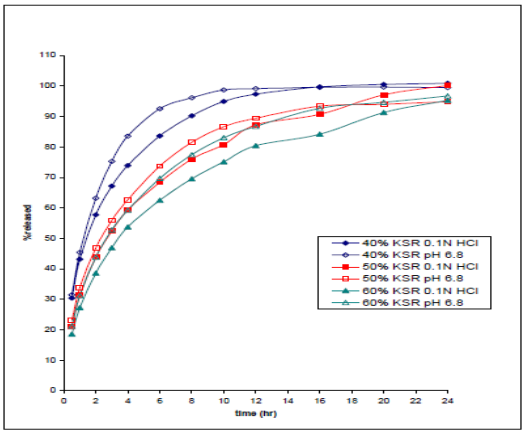

Figure 11: Effect of dissolution medium on drug release from propranolol 80mg tablets.

It was found that the drug release was faster at 40% polymer levels, and further increase from 50 to 60% did not significantly change the release rate. The insoluble polyvinylacetate component of the Kollidon® SR is considered to give a coherent matrix in which the drug is dispersed and the release occurred by diffusion through the pore formed by gradually dissolving povidone. Consequently, the release

rate is dependent on the porosity and tortuosity of the tablets. At lower polymer levels, the diffusion occurred faster due to lower porosity of the matrix, while increasing the polymer concentration led to a slower release until the matrix achieved its maximum tortuosity and minimum porosity. All the tablets remained intact during the 24-hour dissolution test.

3.2.2 Effect of dissolution medium on drug release from propranolol 80mg tablets

Drug release from matrix systems is influenced by the aqueous solubility of the drug and matrix behavior at different pH. Kollidon® SR contains no ionic groups and is therefore inert to drug substances and pH of the dissolution medium. The release rates at every polymer level were virtually pH independent, as confirmed by the almost superimposable release curves in pH 6.8 buffer and 0.1N HCl and f2 values greater that 50 (66.51, 73.38 and 64.95 for Kollidon® SR 40%, 50% and respectively 60%).

3.2.3 Effect of Kollidon® SR – Eudragit® L100-55 combination on drug release from propranolol 80mg tablets

In acidic medium, the enteric polymer is insoluble and acts as a part of the matrix thus contributes to the retardation of the drug release. In buffer media, the enteric polymer dissolves and loosens the matrix structure, thus increasing the porosity and permeability of the dosage form and compensating for the reduction in the diffusion rate. The effect of partial replacement (5 or 10% of the tablet weight) of Kollidon® SR with Eudragit® L100-55, while keeping constant the total matrix forming agent concentration (70% of the tablet weight) was investigated. Eudragit® L100-55 is a methacrylic acid copolymer insoluble at pH below 5.5. As expected, the release rates in water and 0.1N HCl were slightly reduced. This was because Eudragit® L100-55 is insoluble in water or 0.1N HCl, so it acted as a diffusion barrier. Surprisingly, the same phenomenon was observed in pH 6.8 buffer. Possible explanations reside in a hindered dissolution of the enteric polymer due to the polyvinylacetate network

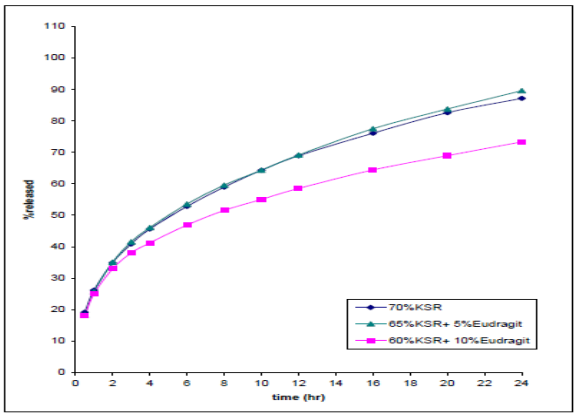

Figure 12: Effect of Kollidon® SR and Eudragit® L100-55 combination on drug release in water from propranolol 80mg tablets

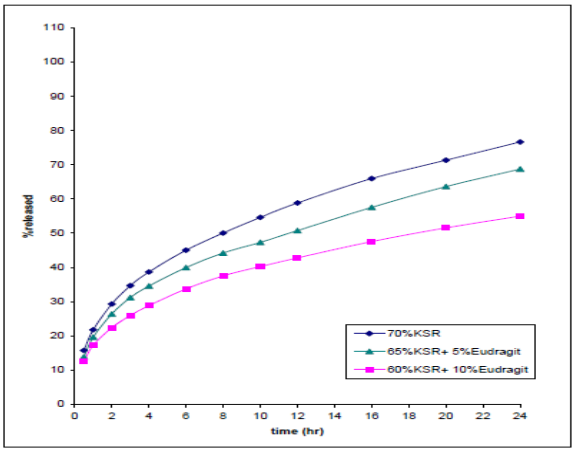

Figure 13: Effect of Kollidon® SR and Eudragit® L100-55 combination on drug release in 0.1N HCl from propranolol 80mg tablets.

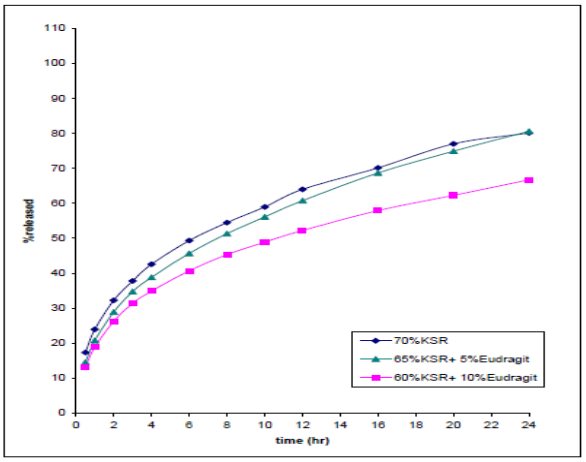

Figure 14: Effect of Kollidon® SR and Eudragit® L100-55 combination on drug release in pH 6.8 buffer from propranolol 80mg tablets.

3.2.4 Comparison of the propranolol 80 mg tablet formulations with the reference listed capsule product

Currently all extended release propranolol products available are capsules and Inderal® LA is the reference listed product (RLD, innovator). The product is formulated as capsules containing coated pellets. Although the condition for pharmaceutical equivalence is not met (due to difference in dosage forms capsules versus tablets), Inderal® LA was used as reference product in developing matrix tablet formulations. By evaluating the release profiles obtained according to the USP dissolution method (method B) for propranolol 80mg tablets with 60 and 70% Kollidon® SR and the reference listed capsule product, it was found that the initial release was faster for the tablets than for the capsules, while at the later dissolution stages the release profile for the innovator product was intermediate to the tablet profiles. Thus, it was decided to formulate and manufacture tablets using an intermediate polymer level (65%).The composition of the selected formulation (65% Kollidon® SR) is presented in Table7. Compared to the reference-listed product, the drug release from the matrix tablets was faster in the initial stage. This can be attributed to differences in the formulation and release mechanism (multiparticulate versus monolithic system). The burst effect observed with the tablets could be explained by the propranolol trapped on the surface of the matrix and released immediately upon activation in the dissolution medium. During the buffer stage, the developed product met the USP requirements for propranolol release and was similar to the innovator product, as determined with the similarity factor (f2=60.60).

Table 8: Characteristics of propranolol 80mg tablets with 65% Kollidon® SR.

Characteristics	*Average*	*RSD*
Tablet weight (mg)	277.91	0.861
Tablet thickness (mm)	4.884	0.308
Tablet hardness(kp)	14.12	4.847
Content uniformity	95.194	2.534

Table 9: Drug release from the propranolol 80 mg tablets with 65% Kollidon® SR.

TIME (hr)	*Propranolol 80mg tablets (65% kollidon® SR)*	*USP Requirments*
1.5	32.69%	NMT 30%
4	49.64%	35-60%
8	62.23%	55-80%
14	77.74	70-95%
24	91.22	81-110%

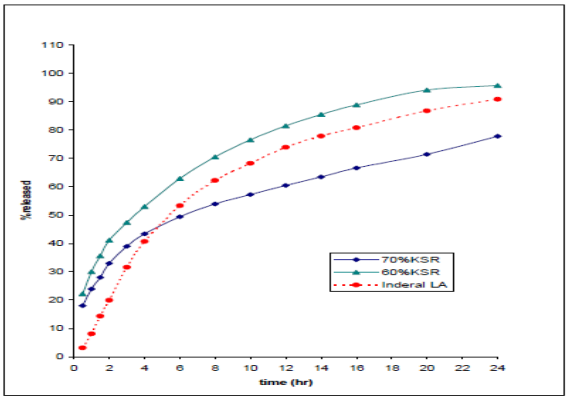

Figure 15: Comparison of drug release from propranolol 80 mg tablets with 60 and 70% Kollidon® SR and Inderal® LA**.**

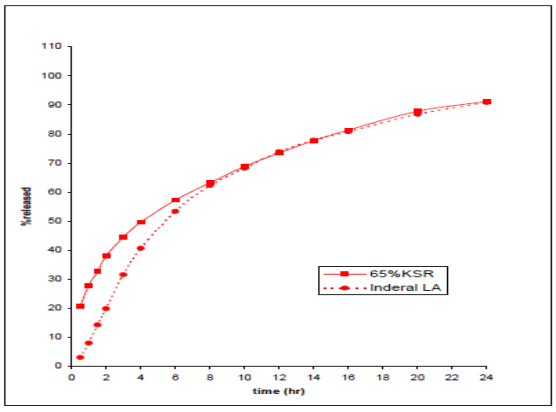

Figure 16: Comparison of the drug release profiles from propranolol 80mg tablets with 65% Kollidon® SR and Inderal® LA.

Table 10: Effect of storage on the hardness of propranolol 80 mg tablets

Time	*25°C/60%RH*	*40°C/75%RH*
Initial	14.12±0.68	14.12±0.68
1 month	15.54±0.43	20.06±0.46* **
3 months	16.39±0.99*	21.06±0.70* **
6 months	16.57±0.63*	29.51±0.32* **
9 months	16.97±0.59*	ND

3.2.5 Effect of storage conditions on propranolol 80 mg tablets physical properties and drug release.

Propranolol 80 mg tablets with 65% Kollidon® SR were tested to see the effect of storage conditions (long term or accelerated ICH testing conditions) on tablet physical properties and drug release (method B). No change in the dissolution profile was observed for tablets stored under long term stability conditions for a period of up to nine months. A change in the dissolution profile was observed for tablets stored at 40°C/75% RH for more than 3 months. The reduction in the dissolution rate continued after six months, the time period recommended for conducting accelerated stability studies; it was also observed at nine months testing point. The change in the dissolution profile observed just in case of the tablets stored under accelerated conditions could be attributed to the amorphous nature of polyvinylacetate coupled with its unusually low glass transition temperature of 28–31°C, which imparts certain unique characteristics to the matrix. The change in the dissolution rate of propranolol tablets was accompanied by an increase in tablet hardness. The increase in hardness was significantly higher for accelerated conditions compared to the long term conditions ($p<0.05$)

4. CONCLUSIONS

A minimum concentration of 30% polymer was necessary to achieve a coherent matrix, able to extend the release of the incorporated drugs. Increasing the Kollidon® SR concentration in the tablet led to an increase in the tablet hardness and a slower drug release. Drug release followed square root of time dependent kinetics, thus indicating a diffusion-controlled release mechanism. Kollidon® SR was the main release controlling agent in the presence of an external binder or enteric polymer in the matrix. A significant reduction in the dissolution rates associated with an increase in tablet hardness was observed during stability testing under accelerated conditions, but not under long term conditions. Based on this finding, the recommended storage conditions are at 25°C / 60%RH or lower. Based on the above, it is concluded that Kollidon® SR is a potentially useful excipient for the production of pH-independent extended release matrix tablets.

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