



STUDY OF EFFECTS OF POST-COMPRESSION CURING ON KOLLIDON® SR BASED FLOATING TABLETS

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ABSTRACT

Floating Kollidon® SR (KSR) matrix tablets containing Labetalol HCl (LBT) were developed and evaluated with respect to in vitro drug release and floating behaviour. Kollidon® SR is amorphous polymer having unusual low glass transition temperature of 29 – 31°C. It was therefore the purpose of this research to study the effects of curing of tablets on tablet properties. Kollidon® SR was able to delay LBT release efficiently. PEG 6000 was used as channeling agent which accelerated the drug release by forming pores in the matrix tablets. Post-compression curing of tablets increased the hardness, decreased the floating lag time and in vitro drug release. Effects of curing on drug release were reduced by increasing the lactose content and by decreasing KSR content.

Keywords: Kollidon® SR, Floating tablets, Channeling agent, Post-compression curing.

INTRODUCTION

Labetalol hydrochloride (LBT) a non selective α , β -adrenoceptor antagonist is used in the treatment of hypertension. It is appreciably soluble in lower and higher pH solutions, with minimum solubility between pH 6 to 10. The drug shows variable bioavailability ranging from 10-80 % which may be attributed to its instability in alkaline pH and poor absorption due to precipitation. It is administered in doses ranging from 50-200 mg twice a day due to its shorter half life of 3-6 h suggesting the need for sustained release formulation.¹ Thus the present study was aimed at developing sustained release gastroretentive dosage form of labetalol hydrochloride.

For the present investigation Kollidon® SR (KSR) was chosen as a matrix forming excipient for floating controlled release formulations. Kollidon® SR consists of 80% water insoluble poly(vinyl acetate) (PVAc) with a molecular weight of about 450,000, 19% water soluble poly(vinyl pyrrolidone), approximately 0.8% sodium lauryl sulphate and about 0.2 % silica as stabilizers.²⁻⁵

It shows excellent flowability and can be used as an excipient for direct compression, whereas these tablets are characterized by a low friability and high crushing forces at low compression forces during the tableting process.^{6,7} With conventional tableting excipients, under so much low pressure either no tablets are produced or the strength of the tablet is so low that it cannot be further processed. Therefore the volume of tablets is high compared with the conventional one and thus density decreases. The plastic behaviour of this combination leads to the retention of high porosity, resulting in the dosage form floating on gastric fluid. When the tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through

which the active ingredient slowly diffuses outwards. Kollidon® SR contains no ionic groups and is therefore inert to drug substances. The sustained-release properties are unaffected by ions or salts.⁸

The amorphous nature of PVAc coupled with its unusually low glass transition temperature (T_g) of 28–31°C imparts certain unique characteristics to this binary matrix⁹. It was therefore the purpose of this research to examine key formulation and process variables that could affect the release kinetics. Effect of formulation variables like concentration of KSR on the floating behaviour and drug release and additional excipients like lactose and PEG 6000 on drug release was studied. Effects of post compression curing of the tablets were also observed.

MATERIALS AND METHODS

Materials

LBT was obtained as a gift sample from Samarth Labs, India. KSR and Kollidon VA 64 (KVA 64) were obtained from Signet Chemical Corporation, Mumbai. Other materials and solvents used were of analytical grade. All the studies were carried out using double distilled water.

Formulation of floating tablets

Floating tablets of LBT were formulated as per the formulations given in Table 1, by direct compression method.

The ingredients were weighed accurately and mixed thoroughly in increasing order of weights for 10 min. After adding magnesium stearate the powder mixture was blended for another 2 min. Batches F1- F12 and F13- F14 were compressed on single punch compression machine using 12 mm flat bevelled and 13 mm standard concave circular punches respectively.

Table 1: Composition of different floating tablet formulation of LBT

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
LBT	100	100	100	100	100	100	100	100	100	100	100	100	100	100
KSR	180	200	220	220	220	220	220	220	220	220	200	180	250	225
KVA 64	--	--	--	10	20	20	20	20	20	20	20	20	25	25
PEG 6000	--	--	--	--	--	12	20	24	28	24	24	24	30	30
Lactose	112	92	72	62	52	40	32	28	24	28	48	68	85	110
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4	5	5
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4	5	5
Total weight	400	400	400	400	400	400	400	400	400	400	400	400	500	500

* All the quantities are in mg

Post compression curing procedure

For curing experiments tablets were stored in an oven at 60°C for 1 hour. Tablets were removed and stored at room temperature overnight and then were evaluated.

Physical characterization of tablets

The tablets were evaluated for diameter, thickness, weight variation, hardness and friability. Thickness and diameter of ten tablets were measured using vernier callipers, hardness with Monsanto tester and friability with Roche type friabilator.

In vitro buoyancy studies

The tablets were placed in 0.1 N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). The total floating time (FT) was also determined.¹⁰

In vitro drug release

The dissolution test was carried out using USP XXIII dissolution testing apparatus II (VDA-6DR USP Veego scientific). The test was performed at a paddle speed of 50 rpm using 900 mL of 0.1 N HCl as the dissolution medium, at 37 ± 0.5°C. An aliquot of 5mL was withdrawn at 1, 2, 3, 4, 6, 9, 12, 18 and 24 h intervals; and the absorbance was measured by using UV-visible spectrophotometer SHIMADZU (Model UV - 1601 Double beam spectrophotometer) at 302 nm.

Effect of osmolarity and pH on floating behaviour

Floating behaviour of tablets was studied at various osmolar conditions and pH. Hyper-osmolar (400 osmoles), iso-osmolar (308 osmoles) and hypo-osmolar (200 osmoles) solutions and buffers of pH 1.2, 4 and 6.8, each 100 ml were used to study the effect of osmolarity and pH on floating behaviour.^{11,12}

Determination of swelling behaviour

The swelling behaviour of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen dimensions of the tablet were determined at different time intervals. The swelling behaviour index was calculated by the following equation:

$$\% \text{ Increase in Diameter} = \frac{\text{Diameter at time t} - \text{Diameter at time zero}}{\text{Diameter at time zero}} \times 100$$

$$\% \text{ Increase in Thickness} = \frac{\text{Thickness at time t} - \text{Thickness at time zero}}{\text{Thickness at time zero}} \times 100$$

RESULTS

Physical characterization of tablets

The diameter of the tablets of batches F1- F12 and F13-F14 were found to be 12 mm and 13mm respectively. The thickness of the tablets of batches F1-F12 and F13-F14 were found to be 4 ± 1 mm and 5 ± 0.5 mm respectively. Tablets of batches F1-F12 and F13-F14 had weight within 400 ± 5 mg and 500 ± 5 mg respectively. Batches F1 and F2 containing 45% and 50% of KSR showed poor physical integrity hence were not studied further. Batch F3 containing 55% of KSR showed good physical integrity but hardness was low (1.5 Kg/cm²) and friability was high (0.85%). Incorporation of KVA 64 as dry binder increased the hardness of the tablets. Batch F4 containing 2.5 % of binder showed hardness of 1.5 Kg/cm² and 0.78 % friability. Batch F5 containing 5% of binder had optimum hardness of 2 Kg/cm² and low friability (0.35%) hence this concentration of binder was used in further batches. For batches F6 - F9, hardness and percentage friability ranged from 2.0 to 3 Kg/cm² and 0.2 - 0.5 % respectively.

Effect of post compression curing

Batches F10 - F14 were subjected to curing to study the effect of curing on hardness and friability of tablets. Table 2 shows the hardness and friability data of batches F10 - F14 before and after

curing of tablets. It was observed that curing of the tablet samples was associated with increase in hardness of tablets. Heating the tablet samples above the *T_g* of the polymer PVAc lead to an increased mobility of the polymer chains, wherein imperfections in the structure of the polymer matrix were equalized, leading to a hardening of the tablets.¹³

Table 2: Effect of curing on tablet hardness and friability

Formulation code	Hardness (Kg/cm ²)	Friability (%)
F10 Before curing	2.5	0.3
F10 After curing	4	0
F11 Before curing	1.5	0.8
F11 After curing	2.5	0
F12 Before curing	1.5	1.1
F12 After curing	2.5	0.5
F13 Before curing	1.5	0.6
F13 After curing	2.5	0.3
F14 Before curing	1.5	0.8
F14 After curing	2.5	0.3

In vitro buoyancy studies

Batches F1 and F2 containing 45% and 50 % of KSR did not float. Batches F3- F9 containing 55% of KSR showed floating for more than 24 hr with no lag time. This indicated that floating behaviour was dependent on KSR concentration. The polymeric structure of Kollidon® SR possesses an enhanced ability to entrap air during the compression process. Higher excipient levels were related to a slightly lower density and thus improved floating behaviour. During the dissolution process LBT will start to dissolve, whereas the water insoluble matrix former Kollidon® SR will begin to swell. Therefore the ability to efficiently entrap the air present in the matrix tablet will improve with increased Kollidon® SR contents.

Effect of post compression curing

Table 3 shows the results of floating behaviour of batches F10 - F14 before and after curing. It was observed that floating behaviour was improved by curing of tablets. Lag time prior to curing in batches F10, F11, F13 and F14 was between 3 to 5 min which was decreased to 0 to 1 min after curing of tablets. Batch F12 containing 45% of KSR did not show floating before curing but floated after curing with lag time of 1 hr. Thus floating behaviour was affected by curing of tablets.

Table 3: Floating behaviour of batches F10 - F14

Formulation code	FLT (min)	FT (h)
F10 Before curing	0	> 24
F10 After curing	0	> 24
F11 Before curing	3	> 24
F11 After curing	0	> 24
F12 Before curing	No floating	--
F12 After curing	1 hour	> 24
F13 Before curing	3	> 24
F13 After curing	0	> 24
F14 Before curing	5	> 24
F14 After curing	1	> 24

In vitro drug release

Fig. 1 and Fig. 2 shows the in vitro drug release profiles of various formulations mentioned in Table 1. Batches F1- F3 did not float and hence were not further tested for in vitro release. Batches F4 and F5 containing 55% of KSR showed incomplete drug release of 76.29% and 75.02% respectively. Batches F6, F7, F8 and F9 containing 3, 5, 6, 7 % of PEG 6000 showed 86.47, 94.47, 98.11 and 77.9 % release respectively at the end of 24 h. Addition of PEG 6000 and increase in lactose concentration lead to significant improvement in drug release. This can be attributed to the good water solubility of PEG 6000 and lactose. Upon contact with the release medium, PEG 6000 and lactose dissolves and diffuses out of the matrix tablet, thereby increasing the porosity of the resulting polymer network. Drug release increased with the concentration of PEG 6000 in concentration range 3 to 6 % but it was retarded at 7% concentration. High molecular weight PEGs increase the drug

release in low concentration by increasing the porosity of the matrix. At high concentration of PEGs, the release is opposed by viscosity of aqueous filled channels which retards the movement of the drug molecules. Similar results have been reported by Kumar *et al* who observed the effects of PEG 4000 and PEG 10000 on release of diazepam from glyceryl monooleate based gastro- retentive matrix carrier system. PEGs increased the release up to certain concentration and decreased thereafter.¹⁴

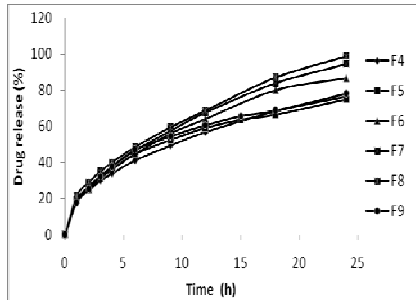


Fig. 1: Comparison of in vitro dissolution profiles of formulations F4 to F9

Effect of post compression curing

When amorphous polymers are heated to temperature above glass transition temperature (T_g), its mechanical properties are influenced. This process is called curing (annealing) which increases the density within the polymer and decreases the rate of stress relaxation at temperature below the T_g . This change tend to improve the dimensional stability of the polymer. Curing process can significantly affect the drug release rate from tablets incorporating polymers which have low T_g .¹³ Omelczuk *et al* has concluded that

curing at temperature above T_g significantly improved film formation which could reduce the permeability of the film and avoid accelerated and irreproducible dissolution results.¹³ KSR which contains 80 % of polyvinylacetate (PVAc) polymer is amorphous in nature and has got unusually a low T_g temperature of 28 - 31°C. When incorporated into tablet dosage form it may undergo curing during the normal processing condition and affect physical integrity and drug release rate.¹⁵ Shao *et al* has reported that post-compression curing step was found to be very critical in stabilizing the release rates of tablets containing high levels (more than 47%) of Kollidon® SR. The curing duration studies concluded that a few hours at 60°C is a sufficient curing condition for such tablets.¹⁵ Thus in order to get tablets with stabilized dissolution pattern and improved physical stability, tablets were subjected to curing at 60°C for 1 hr. Batch F10 – F14 were cured to check the effect of curing on hardness, friability, floating behaviour and drug release of the tablets. Batch F10 containing 55% of KSR showed 98.11% release at the end of 24 h before curing and showed 77.24 % CR after curing. In order to maintain complete dissolution even after curing further batches were taken with decrease in KSR concentration. Batches F11 and F12 containing 50% and 45% KSR respectively showed complete release before curing and after curing drug release was decreased to 80.1 % and 88.7 % at the end of 24 h for batches F11 and F12 respectively. Curing of tablets improved the floating behaviour and hardness but decreased the in vitro drug release. To get complete drug release, lactose concentration was increased from 12% in batch F11 to 17% in batch F13. Batch F13 showed complete release and 95.26% drug release at the end of 24 h, before and after curing respectively. Batch F14 prepared with 45 % KSR and 22% lactose showed complete drug release before curing and drug release of 98.4% after curing of tablets. Further tests were performed on batch F14 as floating behaviour and drug release was optimum for this batch. It was observed that post-compression curing step was found to be critical in stabilizing the drug release from tablets.

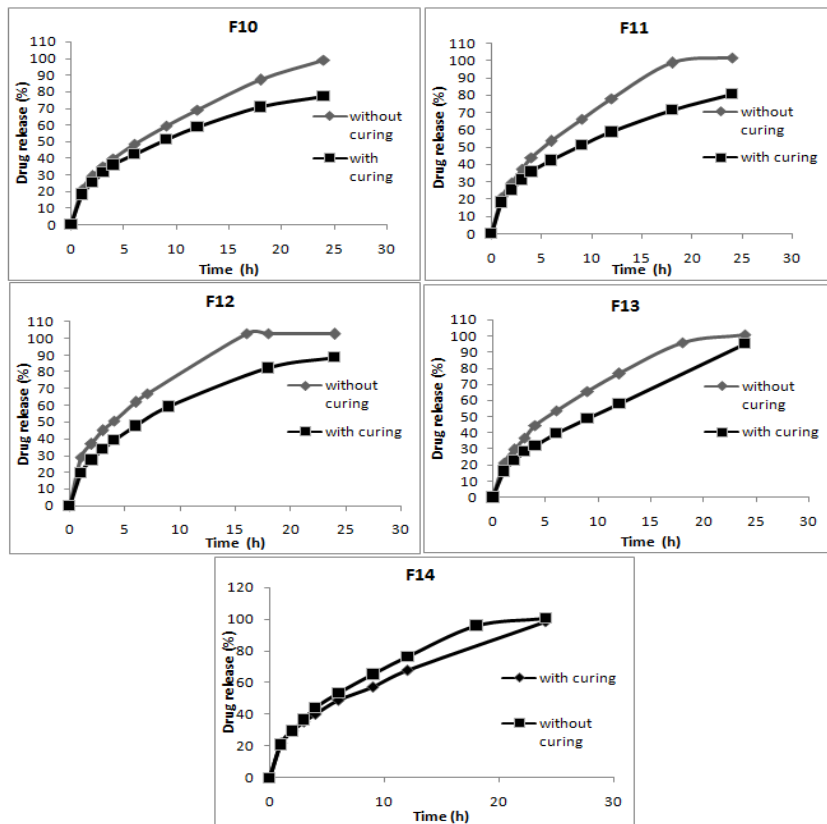


Fig. 2: Comparison of in vitro dissolution profile before and after curing of formulations F10 to F14

Effect of osmolarity and pH on floating behaviour

Effects of change in osmolarity and pH on FLT and FT of batch F14 are shown in Table 4. The results showed that FLT and FT of the formulation was not affected by the variations in osmolarity and pH. Thus it can be concluded that floating behaviour of tablet may not get affected by the changes in osmolarity and pH of the gastric content.

Table 4: Effect of pH and osmolarity on floating behaviour

Medium	FLT (min)	Floating time (h)
0.1 N HCl	1	More than 24h
Buffer pH 1.2	1	More than 24h
Buffer pH 4	1	More than 24h
Buffer pH 6	1	More than 24h
Hypo-osmolar solution (200 mmoles/L)	1	More than 24h
Iso-osmolar solution (308 mmoles/L)	1	More than 24h
Hyper-osmolar solution (400 mmoles/L)	1	More than 24h

Determination of swelling behaviour

Food may induce changes in the environment and osmolarity of the gastric contents, which in turn may affect the swelling behaviour of the formulation and hence the drug release. To eliminate this possibility, swelling behaviour of the formulation was assessed in 0.1 N HCl and different osmolar solutions.

As seen from Fig. 3 and Fig. 4, it was observed that osmolarity or type of medium did not affect the swelling behaviour of the tablets significantly. The tablets showed gradual increase in thickness and diameter up to 10 h and then slight increase up to 24 h. This initial swelling of tablets is because of absorption of aqueous medium and relaxation of polymer upon contact with aqueous media.

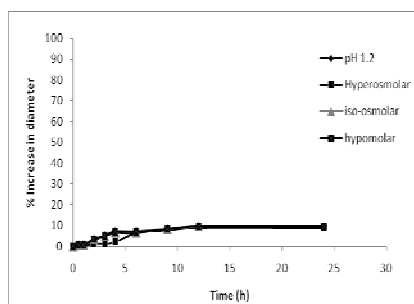


Fig. 3: Results of % increase in diameter of LBT floating tablets

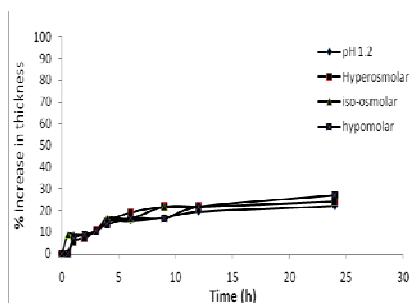


Fig. 4: Results of % increase in thickness of LBT floating tablets

CONCLUSION

The aim of present study was to prepare a formulation of LBT having negligible FLT with gradual release of drug over a period of 24 h with simultaneous floating and to study the effect of post compression curing of tablets. For this purpose Kollidon® SR was

tried which acts as sustained release polymer and also helps in floating of the formulation. To improve the hardness and friability of tablets Kollidon VA 64 was used as a dry binder. PEG 6000 was added as a channeling agent to increase the penetration of the surrounding dissolution medium into tablet by forming pores in the matrix tablets which accelerated the release of drug. Post-compression curing of tablets improved the floating behaviour and mechanical properties but decreased the in vitro drug release. Concentrations of polymer and diluent were important formulation variables in maintaining the in vitro drug release after curing of tablets. Various tests carried out on the optimized formulation proved that there was no significant influence of variations in pH and osmolarity on in vitro buoyancy and swelling behaviour. Thus it can be concluded that the gastroretentive tablets of LBT can be prepared successfully with desired release pattern, negligible FLT and FT of about 24 h using Kollidon® SR as polymer and lactose and PEG 6000 as channeling agent.

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