Research Article

The Effect of Powder Blend on Drug Release Mechanisms of Hydrophobic Starch Stearate Matrix Tablets

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Abstract

Free hydroxyl groups of glucose monomer of starch substituted with steroyl group by chemical modification leads to the formation of starch stearate (SS). Modification changes the nature from hydrophilic to hydrophobic and thus used as controlled release excipient. In present study, SS was evaluated as release modifying polymer and MCC, Lactose, Dicalcium phosphate (DCP) and combinations of these were used to evaluate effect on drug release of Verapamil hydrochloride (VH) and Diclofenac sodium (DS). FT-IR studies of polymer with VH and DS have shown no significant drug:polymer interactions. Decrease in in-vitro drug dissolution was observed with increase in polymer concentration. Cumulative drug released for DS (hydrophobic) was more sustained than hydrophilic drug (VH). Drug release from formulations containing 30%w/w of SS after 8h was 81.61 (for VH) and 25.08% (for DS). DCP retarded drug release more when used alone. After 8h % drug release from formulations containing 30%w/w of SS was 49.86 (VH) and 24.19 (DS). The use of lactose alone increased the drug release and combination of DCP:Lactose in equal proportion with 15 %w/w SS sustained more i.e. 42.62% (VH) drug release at the end of 8h.

1. Introduction

Native and modified starches have been used in tablets as fillers, binders and disintegrant [1]. They consist of two polymers of glucose, i.e., linear amylose and branched amylopectin [2]. In general, native starches are insoluble in water but it swells in contact with water and thus has some disintegrating properties. The sustained-release properties of modified starches, generally based on solvent-activation, have been intensively investigated, example, pre-gelatinized starch [3], cross-linked amylose [4] substituted amylase [5] and short chained amylose (i.e., amylodextrin) [6,7] all have retarded drug release from matrix tablets.

In recent years, a new generation of polymers has been introduced as tablet excipient for the purposes of controlled drug release. Different techniques, such as chemical reactions [8], complexation reactions [9] and grafting [10,11] have been applied to alter native biopolymers by process modifications or substitutions with other compounds and on molecular functional groups. Starches are an interesting group of native biopolymers for these objectives. Native potato starches that are chemically modified with steroyl functional groups are defined as starch stearate (SS). As a glucose monomer contains three free hydroxyl groups that can be substituted, the average degree of substitution can range from 0 up to 3.0. The introduction of steroyl functional groups changes the nature of starch (Stearate) from hydrophilic to more hydrophobic. This modification consequently inhibits the characteristic swelling and gel layer formation of native starches. This increased hydrophobicity of starch stearate makes it a suitable controlled drug release excipient for tablets.

Drug release from tablets compressed from modified starches has been studied widely [5, 12- 13]. Besides the

characteristic first-order drug release kinetics known for matrix tablets, linear drug releases over time also have been reported.[14] In particular, changes in drug release kinetic were related to changes in the physical appearance of a tablet during drug dissolution testing. The literature on erodible polymeric delivery systems shows that various transport mechanisms simultaneously influence the total drug release rate [15-18]. Basically, for sequential processes the slowest, and for parallel processes the fastest step is of main importance. Furthermore, porosity and pore size describing the initial matrix structure are also factors that have distinctive contributions to these processes of drug release from substituted polymer matrix tablets.

The most significant variables that affect the release of drugs from the starch stearate matrix are the particle and powder properties of starch stearate, tablet properties (i.e. porosity), the ratio of drug and starch stearate concentrations in the formulation, and the physicochemical nature of the drug [19-22]. The drug release profile can be governed by adjusting these factors.

Thus main aim of this study was to investigate the effects of drug-excipient interactions in a powder blend and resulting tablet structure on drug release kinetics. The physical behavior in a liquid medium of tablets with starch stearate (degree of substitution 2.7) as a hydrophobic, inert matrix former was related to drug release mechanisms.

2. Materials and methods

2.1 Materials

SSs were prepared by esterification of potato starch with Steroyl chloride. Verapamil HCl (VH) and Diclofenac sodium (DS) were gifted by Alembic Pharma Ltd., India and Zim Laboratories, Nagpur, India respectively. Microcrystalline cellulose, Dicalcium phosphate and Lactose monohydrate were obtained from Chemfield Pharma, India, Finar Chemicals, Ahmedabad, India and Loba Chemie Pvt. Ltd., India respectively. All other chemicals used were of analytical grade and used as received.

2.2 Polymer: drug interaction study

The possible polymer: drug interaction was confirmed by FT-IR study. The samples were prepared by physical mixture of polymer, Starch stearate (SS) with drugs (Diclofenac sodium and Verapamil hydrochloride), the spectra obtained by FT-IR spectrophotometer (FTIR-8001, Shimadzu, Japan) operated with omnic software on sample prepared by KBr press pellet technique were examined.

2.3 Preparation of matrix tablets

After preliminary laboratory trials, matrix tablets each containing 50 mg drug was prepared by a conventional wet granulation technique. The composition of various formulations of the tablets with their codes is listed in Table 1. Granulation was done manually with a solution of calculated quantity of SS in sufficient solvent of methylene chloride. The wet mass was passed through a 14 mesh sieve and air dried. The dried granules were sized by a 20 mesh sieve, mixed and lubricated. Granules thus obtained were compressed into tablets on ten station rotary compression machine (Chamunda Machineries, Ahmedabad, India) at a constant compression force using 8 mm punches. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Table No 1. Composition of Tablet Formulations

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
VH	20	20	20	20	20	20	20	20	-	-	-	-	-
DS	-	-	-	-	-	-	-	-	20	20	20	20	20
MCC	63	58	48	-	-	24	24	-	63	58	48	-	-
LM	-	-	-	48	-	24	-	24	-	-	-	48	-
DCP	-	-	-		48		24	24	-	-	-	-	48
SS	15	20	30	30	30	30	30	15	20	30	30	30	30
MS	2	2	2	2	2	2	2	2	2	2	2	2	2

*VH- Verapamil hydrochloride, DS- Diclofenac sodium, MCC- Microcrystalline cellulose, DCP- Dicalcium phosphate, LM- Lactose monohydrate, MS- Magnesium stearate, SS-starch stearate.

2.4 Evaluation of granules

2.4.1 Determination of Angle of repose:

The angle of repose was determined by fixed height funnel method, where a funnel is fixed to a stand and it is adjusted up to the required height and pellets are filled into the funnel by closing the tip of the funnel with finger [23-25].

After filling the funnel completely the finger is released and pellets are allowed to pass until they form a pile. Then the angle of repose is calculated as shown in Table 2.

2.4.2 Determination of bulk density

The bulk density was measured by taking 50 g of into 100 ml calibrated measuring cylinder and subjected to 3 taps, then bulk density was calculated by calculating the volume occupied then dividing weight by volume

2.4.3 Determination of Tapped density:

The tapped density was measured by dividing weight by volume but the final volume was measured after tapping the cylinder for fixed number of tappings as per the pharmacopeia guidelines until a constant volume was obtained using tap density apparatus (Electrolab®, India) the results are shown in Table 2.

2.4.4 Compressibility index

Compressibility index was determined after determining bulk and tapped density by using the following formula

$$Carr's\ index\ (\%) = [(TD-BD)] / TD \times 100$$

2.4.5 Hausner's ratio

Hausner's ratio was determined by using the following formula

$$Hausner's\ ratio = TD / LD$$

Table No 2. Evaluation of granules

Formulations	Angle of response(θ)	Bulk density(g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	21.41	0.46	0.51	9.80	1.10
F2	20.6	0.38	0.44	13.64	1.15
F3	25.32	0.44	0.47	10.64	1.06
F4	25.97	0.47	0.57	17.54	1.21
F5	25.68	0.57	0.66	13.64	1.15
F6	23.80	0.43	0.51	15.69	1.18
F7	25.23	0.44	0.47	10.64	1.06
F8	24.44	0.57	0.67	14.93	1.17
F9	26.56	0.43	0.47	8.51	1.09
F10	26.07	0.42	0.47	10.64	1.11
F11	26.83	0.51	0.57	10.53	1.11
F12	25.45	0.46	0.52	11.54	1.13
F13	25.20	0.59	0.65	9.23	1.10

2.5 Evaluation of tablets:

2.5.1 Tablet thickness:

Tablet thickness was determined using a screw gauge micrometer and the limit and the variation should be ±5% of the standard value.

2.5.2 Tablet Hardness:

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness (Lachman, 1991). The hardness of the formulated tablets were determined using Monsanto hardness tester.

2.5.3 Friability:

Friability was measured using Roche friabilator (Campbell Electronics, Mumbai, India). It evaluates the ability of the tablet to with stand abrasion during packaging, handling and shipping. Required quantities of tablets were taken based on their weight following the procedure according to USP. Then the tablets were placed in the apparatus and allowed to rotate for 100rpm (4min with 25rpm) [26-28]. Then the tablets were weighed and the loss in weight before rotation and after rotation indicates the friability losses. The generally accepted range is the friability losses should be between 0.5-1.0 % and the results are tabulated in Table 3.

2.5.4 Drug content:

The drug content was determined by crushing the tablets and taking sample equivalent to 100.0 mg from each formulation [29-32]. The sample was transferred to 100.0 mL flask and diluted to volume with the pH 6.8 phosphate buffer

and sonicated for 20 minutes (PCi Mumbai, India), centrifuged and filtered and the drug content was determined from absorbance at its lambda max using UV spectrometer (Shimadzu-UV-150-02 Kyoto, Japan)

2.5.5 *In Vitro* dissolution studies:

The *in vitro* dissolution study was carried out in using USP XXIV dissolution test apparatus type II (Veego Scientifics, Mumbai) at 75 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer 9 h maintained at 37 ± 0.5 ^{0}C. An aliquot (10 ml) was withdrawn at specific time intervals and drug content was determined by analyzing the samples with UV/VIS spectrophotometer (1700 Shimadzu, Japan) at 276 nm for DS and 278 nm for VH.

Table No 3: Evaluation of tablets

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	5.05± 0.003	3.47± 0.252	0.23	98.20 ± 0.572
F2	5.02± 0.001	3.17± 0.289	0.23	97.89± 0.360
F3	5.05± 0.004	3.47± 0.351	0.19	99.10± 0.354
F4	5.02± 0.002	3.37± 0.321	0.22	98.06± 0.459
F5	5.01± 0.006	3.17± 0.289	0.22	98.73± 0.800
F6	5.52± 0.003	3.60± 0.265	0.17	98.77 ± 1.102
F7	5.53± 0.004	3.47± 0.252	0.21	97.40± 0.780
F8	5.54± 0.002	3.10± 0.100	0.24	98.20± 0.633
F9	5.52± 0.001	3.33± 0.351	0.18	98.78± 0.234
F10	5.54± 0.001	4.20± 0.200	0.19	98.98± 0.472
F11	5.50± 0.004	4.17± 0.289	0.23	99.17± 0.471
F12	5.53± 0.002	3.40± 0.100	0.21	99.44± 1.064
F13	5.51± 0.005	3.53± 0.058	0.27	98.80± 0.580

2.5.6 Drug release kinetic model:

To describe the kinetics of drug release from the tablets, mathematical models zero order, first order, Higuchi, Hixon-crowell, Korsmeyer-Peppas were used. The criterion for selecting the best fit model was chosen on the basis of the goodness fit test. Equations previously stated were used to determine the best fit model for release kinetics [16, 33-35].

3. Results and Discussion

3.1 The FT-IR spectra of polymer:

Drug does not show any additional peaks. This indicates that actives used in the studies are compatible with the polymer i.e. starch stearate (Fig. 1). The granules of different formulations prepared were evaluated with respect to angle of repose, bulk density (BD), tapped density (TD) and compressibility index (Table 2). The granules exhibited angle of repose below 27° indicating good flow properties [35-38]. Compressibility index values were in the range of 9.23 to 17.54 %. The results of BD and TD ranged from 0.38 to 0.57 g/ml and 0.44 to 0.67 g/ml respectively. The thickness of all the tablets was in between 5.008 to 5.537 mm. Drug content was found to be uniform among different batches of the tablets and ranging from 97.69% to 99.45%. All the physical parameters of the tablets were well within the range.
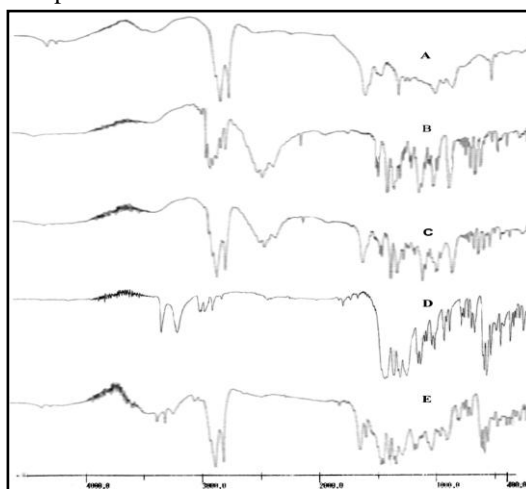

Fig. 1 FT-IR spectra of Starch stearate, drugs and with combination. A, SS; B, VH; C, SS:VH; D, DS, E, SS:DS.

3.2 Effect of concentration of polymer on drug release:

Dissolution profiles shown that with increase in polymer concentration, drug release was decreased. The drug release from F1, F2, F3, F9, F10 and F11 after 8h was found to be 94.12%, 86.10%, 81.60%, 39.67%, 32.12% and 25.08% respectively shown in Fig. 2 and 5.
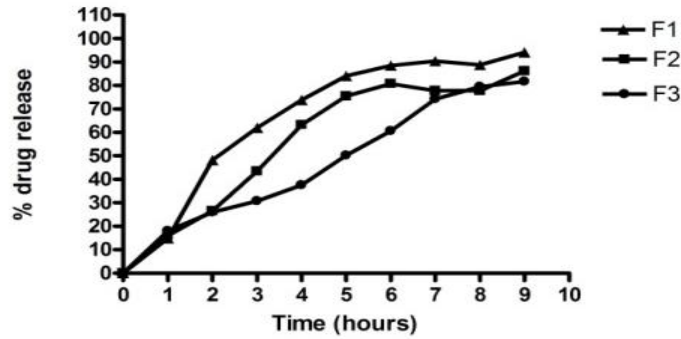

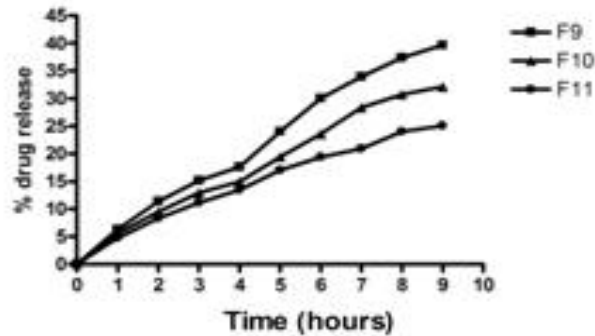**Fig. 2 Comparative drug release profile of F1 to F3**

Fig. 5 Comparative drug release profile of F9 to F11

3.3 Effect of drug properties on drug release

As observed from the cumulative drug release data, hydrophobic drug (DS) was more sustained than hydrophilic drug (VH). Drug release from F3 and F11 after 8h was 81.605 and 25.08% respectively.

3.4 Effect of excipient on drug release

Different excipients such as MCC, lactose and DCP were used for studying their effect on drug release. It was noticed that DCP sustained drug release more than others when used alone. After 8h, % drug release from F5 and F13 was 49.86% and 24.19% respectively. When lactose was used alone with hydrophobic drug (F12), drug release increased (48.81%). This may be due to formation of pores during the drug release. Effect of combination of excipients in equal proportion was also studied on hydrophilic drug and it was observed that combining the DCP and lactose (F8) sustain more i.e. 42.62%. Comparison of drug release effects of excipients both alone and in combination is shown in fig 2 to 6.
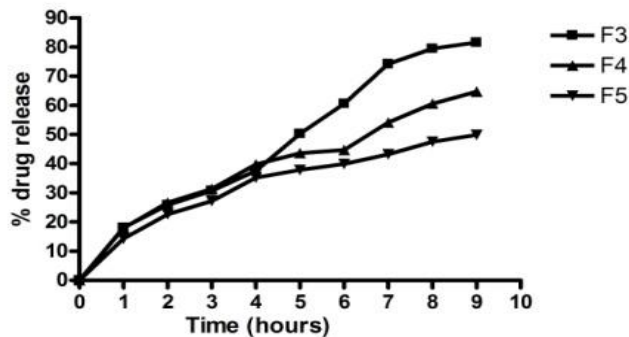

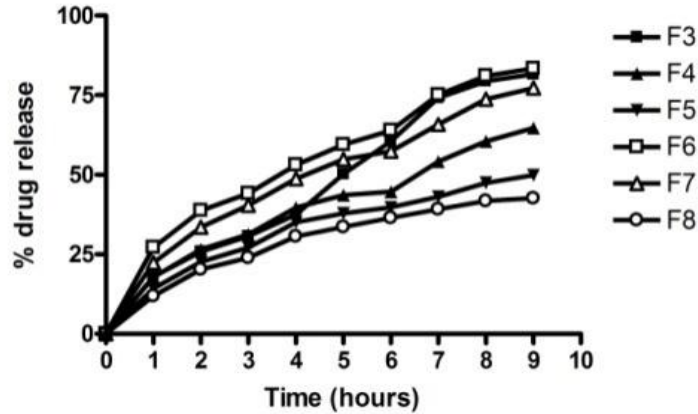
Fig. 3: Comparative drug release profile of F3 to F5

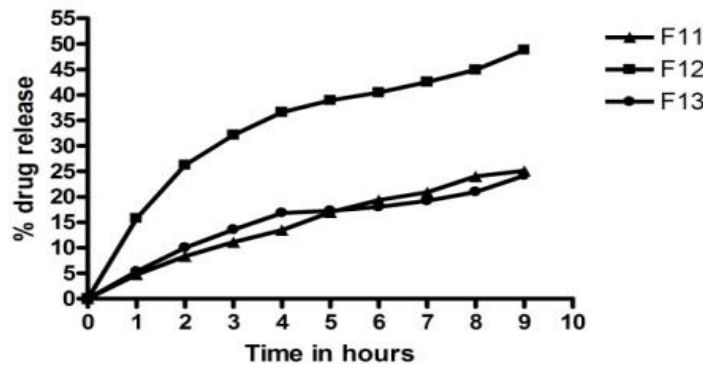**Fig. 4 Comparative drug release profile of F3 to F8**

Fig. 6 Comparative drug release profile of F11 to F13

3.5 Drug release kinetics:

Dissolution profiles were used to asses differences between tablet formulations and to demonstrate the versatility of Drug/SS drug-delivery systems. In general, drug release from formulation containing 30% SS concentration was more sustained than other once [39-40]. Drug release parameters of different formulations are given in Table 4.

Table No 4: Drug release kinetics

Formulation	Best Fit model	N	R
F1	First order	0.763	0.983
F2	Korsmeyer-peppas	0.801	0.972
F3	Zero order	0.740	0.986
F4	Korsmeyer-peppas	0.576	0.994
F5	Higuchi	0.561	0.995
F6	Higuchi	0.517	0.997
F7	Korsmeyer-peppas	0.559	0.998
F8	Higuchi	0.577	0.996
F9	Hixon.Crowell	0.858	0.996
F10	Korsmeyer-peppas	0.820	0.996
F11	Korsmeyer-peppas	0.765	0.999
F12	Higuchi	0.475	0.990
F13	Higuchi	0.627	0.988

4. Conclusion

Starch stearate was shown to be a suitable material to control the release of both hydrophilic and hydrophobic drug. This study further confirmed that diffusion was the predominant release mechanism, as the n value of different formulations is less than 0.89.

Acknowledgement

Authors would like to thank Alembic Pharma Ltd. (India) and Zim Laboratories, Nagpur (India) for providing gift sample of actives. Authors are also thankful to the UGC for financial assistance and Head of the department of Department of Pharmaceutical Sciences RTM Nagpur University, Nagpur for providing necessary facilities.

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