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Direct compression of cushion layered ethyl cellulose coated extended release pellets into rapidly disintegrating tablets

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ABSTRACT

The aim of this study was to develop and optimize cushion layered ethyl cellulose coated extended release pellets into rapidly disintegrating tablets without changes in the release profile. In order to avoid segregation problems resulting from particle size differences between coated pellets and excipients and to protect the integrity of brittle ethyl cellulose coating during compression the tabletting excipients were layered on to the ethyl cellulose (6%) coated metoprolol succinate pellets. However, the drug release from these cushion layered pellets increased upon compression. Incorporation of a glidant (magnesium stearate) between the cushion layer and ethyl cellulose coating reduced the compression effect on the drug release. Glidant was coated to a coating level of 1-3%. The F_2 values of optimized formulation (directly compressed cushion layered formulation with 3% magnesium stearate) was found to be greater than 50 and showed similar release as that of uncompressed pellets. The directly compressed cushion layered pellets protected the pellet coating significantly better from damages during compression when compared to the conventional compression of coated pellets and also facilitated segregation free compression of an extended release ethyl cellulose coated pellets in to fast disintegrating tablets.

KEY WORDS: Ethyl cellulose coating, magnesium stearate, extended release, multiparticulate pellets, metoprololol succinate.

INTRODUCTION

Multiparticulate drug delivery systems are the dosage forms which consists of large number of small discrete units each exhibiting desired characteristics that are combined to form one dosage form. e.g. pellets, granules, sugar beads, minitablets etc. Drug particles may be entrapped within the multiparticulates (matrix system) or layered around them (reservoir system). Depending on the type of coating material used sustained release, delayed release or controlled release can be achieved. The purpose of designing the multiparticulate drug delivery system is to develop a formulation with all advantages of single unit formulation[1].

Multiunit pellet system is administered orally either by filling into hard capsules or by compressing in to rapidly disintegrating tablets[2]. Compaction of pellets as rapidly disintegrating tablets becoming more and more important on the pharmaceutical market as they provide several advantages compared to pellet filled capsules and single unit dosage forms. Compared to capsules, tablets are mechanically stronger and produced at lower cost[3].

Compression of coated pellets is a challenging task as the polymer coating may not withstand the compression force that causes the rupture of coating and the drug release may vary[4]. The extent of coating damage depends on the mechanical properties of the polymer coating and the compression force[5]. The polymers that are brittle are more prone to the damage during the stress conditions leading to the loss of extended release properties e.g, ethyl cellulose. Compression into a no disintegrating or slow disintegrating tablet is also undesirable, since pellets are not well separated a very low rate of drug release than the target might be obtained[6].

Generally pellets are blended with tabletting excipients in powder form and then compressed. The admixed tabletting excipients protect the polymer coated pellets and may reduce the damage of coated pellets[7]. However, the difference in the pellet and excipient particle size increases the risk of segregation during the tabletting process and hence variations in weight and drug content occur[5,8]. In order to

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avoid this segregation cushioning agents (filler, disintegrant and sometimes glidant) were either granulated or layered on to the pellets[3]. The disintegration behaviour strongly depends on the composition of the cushion layer. Super disintegrants are used in order to achieve the rapid disintegration of the tablets. Eg: croscarmellose sodium, sodium starch glycolate etc.

Layering of excipients directly on the drug coated pellets followed by compression of these pellets without further addition of excipients results in segregation free compression of coated pellets into tablets with sufficient hardness, disintegration time and without significant changes in the release profile[2,6].

MATERIALS AND METHODS

Materials

Metoprolol succinate was obtained as a gift sample from Aurbindo Laboratories, Hyderabad. Sucrose beads were purchased from Homeocare, Hyderabad. Microcrystalline cellulose (Avicel PH101), Croscarmellose sodium (Ac-Di-S0l) and magnesium stearate were obtained from SD Fine Chemicals Ltd, Mumbai. Ethyl cellulose was obtained from Qualikem Laboratory. Hydroxyl propyl methyl cellulose was obtained from Oxford Laboratory.

Methods

Preparation of directly compressed cushion layered pellets[2,9,10]

Preparation of drug cores

Metoprolol succinate and HPMC as binder (18% w/w solid contents of drug and polymer) were dissolved in solvent system of isopropanol/water (50:50 w/w) and layered on 60g sucrose cores to achieve 10% drug content based on the resulting pellets in a coating pan.

Preparation of coated pellets

Drug layered pellets were coated with 6% ethyl cellulose prepared in solvent system of isopropanol/water (88:12 w/w).

Preparation of top coated pellets

Seal coating

Ethanolic solution of 6% HPMC was sprayed on ethyl cellulose coated pellets as seal coat to a coating level of 2-3% w/w.

Coating of Glidant layer

Ethanolic suspension of magnesium stearate (0%, 0.5%, 1.5% and 3%) containing HPMC as the binder was sprayed on the seal coated pellets. The suspension was prepared to have 6% w/w solid contents that includes magnesium stearate and HPMC as binder in which binder was 25%w/w to the total weight of magnesium stearate). The glidant layer coating was applied with intermittent drying to a level of 1-3%.

Preparation of Cushion layer

Etanolic solution of tabletting excipients such as filler and disintegrant was layered on ethyl cellulose coated pellet or on seal coated pellet or on the glidant coated pellets before compression. Ethanolic solution of excipients was prepared to have 18% w/w solid content that includes excipients and HPMC as binder and the amount of binder was calculated as 10% based on total weight of coated pellets. This solution was sprayed on the pellets to a coating level of 20-100% w/w.

Table 1: Formulae of Various Metoprololol Succinate Formulations

F1	Uncompressed cushion layered pellets without magnesium stearate.
F2	Uncompressed cushion layered pellets with 0.5% magnesium stearate.
F3	Uncompressed cushion layered pellets with 1.0% magnesium stearate.
F4	Uncompressed cushion layered pellets with 3% magnesium stearate.
F5	Compressed cushion layered pellets without magnesium stearate.
F6	Compressed cushion layered pellets with 0.5% magnesium stearate.
F7	Compressed cushion layered pellets with 1% magnesium stearate.
F8	Compressed cushion layered pellets with 3% magnesium stearate.
F9	Compressed cushion layered pellets with 3% HPMC.
F10	Uncompressed conventional pellets with 3% magnesium stearate.
F11	Compressed conventional pellets without magnesium stearate.
F12	Compressed conventional pellets with 3% magnesium stearate.

Total tablet weight is 500mg

EVALUATION OF DIRECTLY COMPRESSED CUSHION LAYERED PELLETS[11]

Pre-compression parameters

The pellets were evaluated for angle of repose, bulk density, tapped density, carr's index, and Hausner's ratio.

Angle of Repose (θ)

The frictional force in a loose powder or granules can be measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

$\theta = \tan^{-1}(h/r)$

Where,
θ is the angle of repose
h is height of pile
r is radius of the base of pile

A funnel was fitted to the brim and the test sample was allowed to flow smoothly Height of the pile and radius of the pile were measured and thereby evaluating the flow ability of the granules.

Different ranges of flow ability in terms of angle of repose are given in table 2.

Table 2. Angle of repose

Angle of repose	Flow
>25	Excellent
25-30	Good
30-40	Passable
<40	Very poor

Bulk Density

Loose bulk density (LBD) and tapped bulk density (TBD) of coated pellets were determined using bulk density apparatus. Accurately weighed 25 g of coated pellets was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14 ± 2 mm. The tapped volume was measured to the nearest graduated unit. The tapping was repeated additional 200 times. Again the tapped volume was measured to the nearest graduated unit. The LBD and TBD were calculated in g per cc using following formula.

LBD = weight of the coated pellets / volume of the packing
TBD = weight of the coated pellets / tapped volume of the packing

Compressibility Index (carr's index)

The compressibility index of the granules was determined by carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is shown in below table 3

Table 3: Specifications of Carr's index

% Compressibility	Flowability
5-12	Excellent
12-16	Good
18-21	Fair Passable
23-35	Poor
33-38	Very poor
<40	Very Very poor

Hausner's ratio

The Hausner's ratio of the coated pellets was determined by the following equation. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Hausner's ratio = TBD / LBD

SEM analysis

The coated pellet was cross sectioned vertically and horizontally and subjected to SEM analysis. The cross sectioned area was viewed for the various layers.

Post-compression parameters

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content, disintegration time and *in vitro* drug release studies.

Thickness

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by vernier caliper.

Hardness

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. "Hardness factor" i.e the average of the six determinations was determined and reported. The force was measured in kilograms per centimeter square.

Friability

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test was performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0%. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

$$Friability\ (\%) = \frac{initial\ \ weight - final\ \ weight}{initial\ \ weight} \ x\ 100$$

Weight uniformity

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±5%) since the total weight of tablets formulated was 500mg. The percentage deviation for weight uniformity of tablets as per IP limits is shown in table 4

Table 4: Weight variation tolerance

Average weight of tablet	Percentage deviation
80 mg or less	±10
More than 80 mg and less than 250 mg	±7.5
250 mg or more	±5

Drug content

Ten tablets were weighed and average weight was calculated. All the 10tablets were crushed in mortar. The powder equivalent to 100mg of metoprolol succinate was dissolved in 100ml of phosphate buffer pH 6.8 and shaken for 20min. Solution was filtered and 1ml of the filtrate was diluted to 100ml using phosphate buffer pH 6.8. Absorbance of resultant solution was measured at 224nm using phosphate buffer pH 6.8 as a blank. The amount of drug present in one tablet was calculated.

***In vitro* disintegration time**

The disintegration time was measured using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket and run the apparatus using phosphate buffer pH 6.8 maintained at 37ºC ± 0.5ºC as the immersion liquid. The assembly should be raised and lowered between 100 cycles per minute. The time in seconds taken for complete disintegration of the tablet without palpable mass remaining in the apparatus was measured and recorded.

***In vitro* dissolution time**

Dissolution of the tablets of each batch was carried out using USP type-II apparatus. The dissolution testing was done in a medium consisted of 500mlof phosphate buffer pH 6.8 for 12h, maintained at 37°C ± 0.5°C and the paddle rotation speed was set at 50rpm. 5ml of the sample was withdrawn for every 1h up to 12h and the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength of 224 nm using double beam UV-Visible spectrophotometer. The content of the drug was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated.

Similarity Factor[2,10]

The compression effect on the tablet was assessed by comparing the release profile of uncompressed and compressed pellets by using similarity factor F_2.

$$F_2 = 50 \log\{[(R_t - T_t)^2]^{-0.5} \times 100\}$$

R_t and T_t are the percentage dissolved at time t for uncompressed (reference) and compressed (test) pellets. n is the number of sampling time intervals. W is the optional weight factor.

Treatment of dissolution data with different release kinetics[3,10]

The dosage forms that do not disaggregate and release the drug slowly (assuming that the area does not change and no equilibrium conditions were obtained) could be represented by zero order kinetics equation. It suggested that the quantity of drug released from the tablets was often analyzed as a function of the square root of time, which was typical for systems where drug release was governed by pure diffusion. To analyze the mechanism of drug release from the directly compressed cushion layered tablets, the data obtained from the drug release studies was analyzed according to the following equations,

1. Zero order model: [$Q = K_0 t$]
2. Higuchi model: [$Q = K_H t^{½}$]
3. Korsmeyer -Peppa's model: $F = (M_t/M) = K_m t^n$
4. First order model:[$Q=Q_O e^{-kt}$]
5. Hixson - Crowell model:[$Q_O^{1/3}-Q^{1/3}=kt$]

In all mathematical equations, Q is the amount of drug released at time t, M_t is the drug released at time t, M is the total amount of drug in the dosage form, F is the fraction of the drug released at time t, K_0 is the zero order release rate constant, K_H is the Higuchi square root of time release rate constant, K_m is constant which depends on the geometry of the dosage form and n is the diffusion exponent indicating the mechanism of drug release. The value n = <0.45 indicates Fickian diffusion, the value of n between 0.45 and 0.89 indicates non-Fickian diffusion and the value n = 0.89 indicates case-II transport.

Stability studies[11,12]

A study on stability of pharmaceutical product was essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. From the point of view of safety to patient it was important that the patient receives a uniform dose of the drug throughout the shelf life of the product. The formulation stored at elevated temperatures such as 40^{0}C ± / 2^{0}C / 75% ±/ 5% RH for 3 months. The samples were withdrawn at end of 3 months checked for drug content.

RESULTS AND DISCUSSION

Evaluation of directly compressed cushion layered pellets

The following table shows changes in weight of pellets after various steps of coating such as seal coating, glidant coating and cushion layer

Table 5: Change in weight of pellets after various steps of coating

Formulation code	Initial weight (gm)	After drug coating (gm)	After polymer coating (gm)	After glidant coating (gm)	After seal coating (gm)	After coating of cushioning excipients (gm)
F1	5	6.5±0.03	7.22±0.02	-	-	14.44±0.02
F2	5	6.5±0.01	7.22±0.01	7.25±0.04	-	14.43±0.02
F3	5	6.5±0.04	7.22±0.05	7.29±0.02	-	14.42±0.01
F4	5	6.5±0.04	7.22±0.03	7.43±0.03	-	14.44±0.04
F5	5	6.5±0.02	7.22±0.03	-	-	14.44±0.05
F6	5	6.5±0.03	7.22±0.01	7.25±0.01	-	14.43±0.04
F7	5	6.5±0.02	7.22±0.03	7.29±0.05	-	14.42±0.05
F8	5	6.5±0.01	7.22±0.02	7.43±0.04	-	14.44±0.01
F9	5	6.5±0.03	7.22±0.02	-	7.44±0.04	14.45±0.02
F10	5	6.5±0.04	7.22±0.01	-	-	-
F11	5	6.5±0.01	7.22±0.03	-	-	-
F12	5	6.5±0.03	7.22±0.04	-	-	-

Pre-compression parameters

The parameters such as weight of pellets after each coating, bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were determined and the results were reported, as shown in Table 6. The pre compression parameters were more or less same for the pellets of all formulations. The angle of repose was found to be 25±0.02º. The bulk density and tapped density were found to be 0.44±0.06 gm/cm3 and 0.516±0.01 gm/cm3 respectively. The carr's index and hausner's ratio were found to be 14.34±0.03 % and 1.16±0.01 respectively. All these results indicate that the pellets possessed excellent flow properties.

Table 6. Pre-compression parameters of the pellets

Parameter	Observation
Angle of repose	25±0.02º
Bulk density	0.44±0.06 gm/cm^3
Tapped density	0.516±0.01 gm/cm^3
Carr's index	14.34±0.03 %
Hausner's ratio	1.16±0.01

SEM analysis:

SEM analysis revealed the structure of cross sectioned pellet. The layers of drug, polymer and cushion layer were seen in the fig 1.

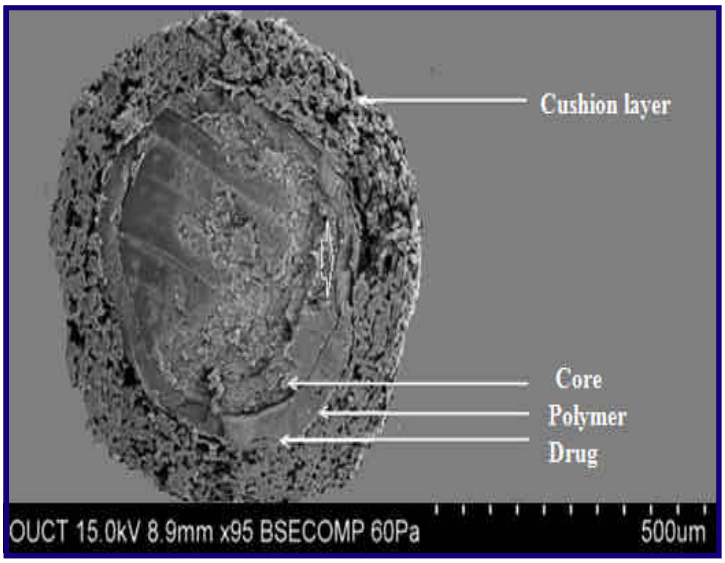

Fig 1. SEM structure of directly compressed cushion layered pellet.

4.2.Post compression parameters:

Properties of tablets such as thickness, hardness, friability, weight variation, drug content and disintegration for the formulations F1 to F12 were determined and the results were reported, as shown in table 7 and 8. The thickness of the tablets was found to be in the range of 4.0±0.01 to 4.3±0.02 mm. According to the weight variation test in IP, the percentage deviation of the tablets weighing above 250 mg was ±5%. The weight of all tablet formulations was as per the official requirements. Good uniformity in drug content was found among different formulations and the drug content was more than 95% for all the formulations. The hardness of the tablets was found to be in the range of 3.9±0.02-4.6±0.004 kg/cm^2. Tablet hardness was not an absolute indicator of strength. Another measure of tablet's strength was friability. Compressed tablets that lose less than 1% of their weight are generally considered accepted. In the present study, the friability for all the formulations was below 1% indicating that the friability was within the prescribed limit. The disintegration time of the tablets was found to be in the range of 9±0.0-13.15±0.03 min. The increase in disintegration time of the formulations was observed with increase in glidant concentration.

Table 7. Results of Post Compression Parameters of the Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Disintegration time (min)
F5	4.3±0.02	4.6± 0.04	0.66±0.02	502±0.02	9±0.01
F6	4.0±0.01	4.4±0.03	0.71±0.04	499±0.01	9.22±0.02
F7	4.3±0.02	4.3±0.02	0.82±0.03	498±0.01	11.45±0.04
F8	4.2±0.01	3.9± 0.02	0.94±0.02	503±0.03	13.15±0.03
F9	4.1±0.02	4.1± 0.02	0.88±0.04	501±0.02	12.12±0.01
F11	4.3±0.01	4.5± 0.02	0.68±0.03	498±0.03	9.11±0.02
F12	4.3±0.02	4.0± 0.02	0.87±0.05	499±0.03	13.05±0.03

Table 8. Drug content of the Compressed/Uncompressed Pellets

Formulation code	Drug content (%)
F1	99.45±0.02
F2	99.94±0.03
F3	99.63±0.02
F4	99.56±0.02
F5	97.98±0.03
F6	98.85±0.02
F7	99.12±0.03
F8	99.46±0.02
F9	97.92±0.03
F10	99.97±0.02
F11	99.62±0.03
F12	98.98±0.02

Dissolution profile of directly compressed cushion layered tablets:

Primarily first four formulations were formulated with varying concentrations of magnesium stearate ((0%,0.5%,1%,3%))and showed desired release. F5,F6,F7 and F8 were formulated with varying concentrations of magnesium stearate that were directly compressed. The addition of magnesium stearate reduced the changes in the release profile between the compressed and uncompressed cushion layered pellets. The corresponding F_2 values were 15.5, 20.54, 27.65, 70.9 for 0, 0.5, 1, 3% respectively. Drug release profiles of formulation (F8) with 3% magnesium stearate could thus be considered similar. (F_2>50) as shown in fig 2.

Formulation F9 was prepared with 3% HPMC as a seal coating between ethyl cellulose coat and MCC based cushion layer. Replacement of magnesium stearate with HPMC seal coating resulted in much lower F_2 values and thus in a more pronounced coating damage dur-

ing tabletting. The glidant layer was thus more effective for the protection of functional coating during compaction compared to HPMC seal coatings as shown in fig 3.

F10, F11, F12 were formulated. F10 was uncompressed conventional pellets with 3% magnesium stearate where as F11 and F12 were compressed conventional pellets with 0 and 3% magnesium stearate. Compressed conventional resulted in accelerated drug release. The F_2 values were much lower when compared to the directly compressed cushion layered pellet formulation. Directly compressed cushion layered formulation was more effective in protecting the integrity of the polymer when compared to the conventional pellet compression as shown in fig 4.

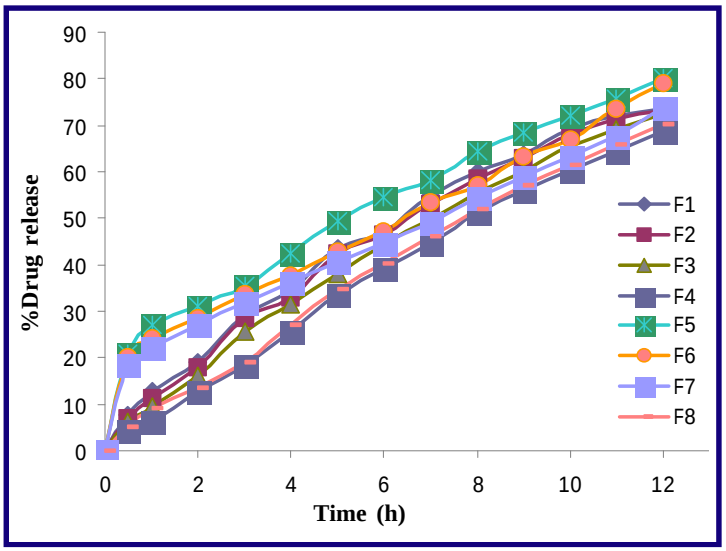

Fig 2. Influence of magnesium stearate on metoprolol succinate release from uncompressed/compressed cushion layered pellets.

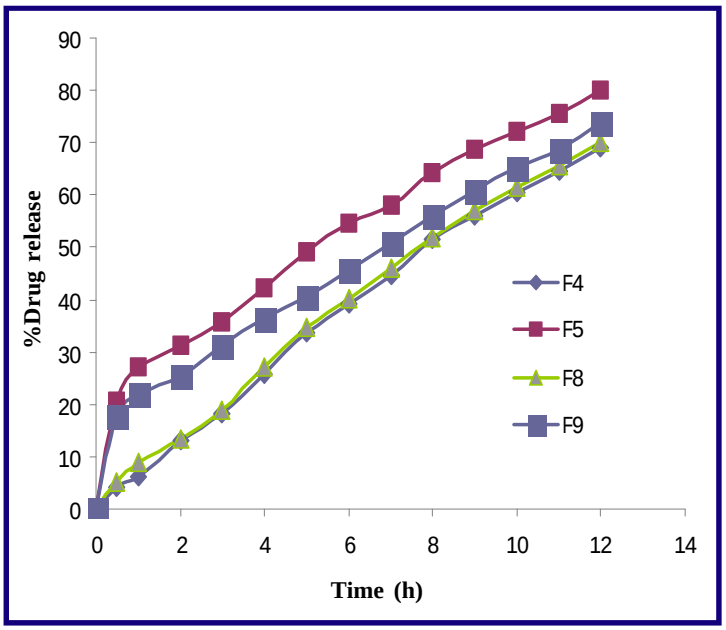

Fig 3. Influence of seal or glidant layers between the ethyl cellulose coat and MCC based cushion layer on metoprolol succinate release.

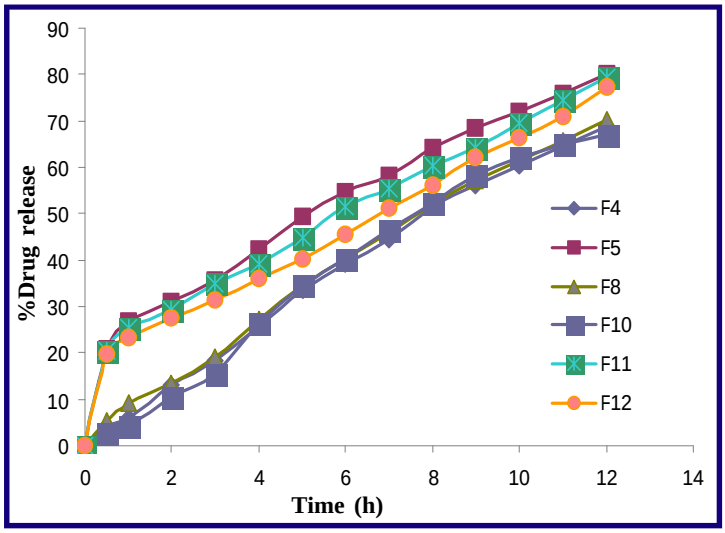

Fig 4. Metoprolol succinate release from conventionally compressed coated pellet and directly compressed cushion layered pellets

4.3. Treatment of dissolution data of formulations with different release kinetics:

Dissolution data of all the formulations was treated with release kinetics and the results were reported, as shown in table 8.The results indicated that the optimized formulations (F4, F8, F10) followed zero order kinetics. The n values of optimized formulations F4, F8, F10 were 0.829, 0.811 and 0.846 respectively. This indicates that optimized formulations followed non-Fickian diffusion.

Table 9. Release kinetics of formulations

Formulation	Zero order K_0 (mg/hr)	R^2	First order K_1 (hr $^{-1}$)	R^2
F1	6.741	0.9845	-0.007	0.9959
F2	6.695	0.9866	-0.007	0.9967
F3	6.469	0.9918	-0.007	0.9962
F4	6.190	0.9970	-0.006	0.9820
F5	6.111	0.9345	-0.008	0.9833
F6	5.558	0.9384	-0.007	0.9752
F7	5.224	0.9383	-0.007	0.9762
F8	6.180	0.9960	-0.007	0.9820
F9	5.527	0.9522	-0.007	0.9808
F10	6.599	0.9933	-0.007	0.9885
F11	5.773	0.9367	-0.007	0.9791
F12	5.479	0.9434	-0.007	0.9696

Formulation	Higuchi K (mg/hr $^{-1/2}$)	R^2	Peppas N	R^2
F1	23.189	0.9123	0.742	0.9942
F2	22.967	0.9383	0.775	0.9946
F3	22.061	0.9129	0.808	0.9928
F4	20.773	0.9882	0.829	0.9889
F5	21.738	0.9856	0.371	0.9639
F6	19.657	0.9849	0.336	0.9732
F7	18.517	0.9854	0.352	0.9816
F8	20.812	0.9841	0.811	0.9857
F9	19.419	0.9622	0.371	0.9663
F10	22.010	0.9932	0.846	0.9874
F11	20.474	0.9845	0.351	0.9615
F12	19.232	0.9713	0.319	0.9637

K_0- Zero order rate constant, K_1- First order rate constant, K- Higuchi model rate constant and R^2-Correlation coefficient.

4.4. Stability studies:

The optimized formulation F8 stored at elevated temperature as 38^0C /± / 2^0C and 70% ± 2^0C

Table 10. Stability studies of F8 at 40^0C /± / 2^0C / 75% /±/ 5% RH

Formulation F8	0 Month	1st month	2nd month	3rd month
Hardness (Kg/cm^2)	4.2 ± 0.01	4.2 ± 0.08	4.1 ± 0.02	4.1 ± 0.05
Drug content (%)	99.46 ± 0.02	98.87 ± 0.01	98.87 ± 0.04	98.67 ± 0.03

5% RH for 3 months. The results of stability studies revealed that there were no changes in the physical appearance, hardness and drug content. The results were shown in table 10.

CONCLUSION

The F_2 value of the directly compressed cushion layered formulation was found to be greater than 50 and thus it was concluded that the cushion layer protected the polymer coating from damage during the compression and showed similar release as that of the uncompressed pellets. Addition of the glidant reduced the pellet rupturing during compression. The directly compressed cushion layered pellets protected the pellet coating significantly better from damages during compression when compared to the conventional compression of coated pellets and also facilitated segregation free compression of an extended release ethyl cellulose coated pellets in to fast disintegrating tablets.

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