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Formulation and Evaluation of Bilayer Tablet by Wet Granulation

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ABSTRACT:

The objective of this present study was to design bilayer tablet of two different drugs for separate release, evaluation of the same and comparison dry granulation formulation with minor changes in components. Both layer of bilayer tablets comprised control release. In wet granulation different type and amount of polymer were used for each layer. The formulated bilayer tablets were evaluated for pre compression as well as post compression parameters including *invitro* dissolution study were carried out. The results showed that wet granulation of formulated bilayer tablet carried out with different polymers viz. Gum acacia, Guar gum, Acrypol -971, HPMC K100M, eudragit RSPO was carried out and based on its release retarding properties. Based on drug release and release kinetics study final formulation was selected that was further analysed for stability study. The accelerated stability study for 6 month showed affirmative results

KEY WORDS: Bilayer tablet formulation, fixed dose combination, drug release kinetics, stability study.

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INTRODUCTION:

Despite fantastic advances within the inhalable, injectable, percutaneous, nasal and alternative routes of administration, the inevitable truth is that oral drug delivery remains well previous the pack because the most popular route. There are of course several applications and enormous markets for non-oral product and also the technologies that deliver them. However, if it's a viable possibility, oral drug delivery are chosen all told however the most

exceptional circumstances. Moreover, if the oral route isn't in real time viable, pharmaceutical firms can typically invest resources in creating it viable, instead of large for another delivery system. Oral route of drug administration have wide acceptance up to 50-60% of total indefinite quantity forms and is that the most convenient and most popular route for systemic effects because of its easy dosing administration, pain rejection, correct dose, patient compliance and adaptability in formulation.

The oral drug delivery market is that the largest section of the drug delivery market and there's no sign that it's swiftness down. With pharmaceutical firms progressively turning to drug delivery to increase the revenue-earning period of their biggest product, and seeking to faucet into the growing older population that needs product with level of ease- of-use and value profit, it's no surprise that the oral delivery drug market may be a $35 billion trade and expected to grows very much like tenth part annually. Oral delivery provides

the definitive break down of the marketplace for oral delivery drug markets. Bilayer tablets unit composed of two layers of granulation compressed together. They appeared like sandwich with two distinct layer and many times different distinctive colour may be used for individual identity. Also colouring the separate layers provides many prospects for distinctive pill identity. Separation of the layers before assay may simplify the analytical work. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) gift no operative problems aside from those common to keyed tooling.

Several pharmaceutical production unit currently developing bilayer tablets, for several of reasons viz. patent extension, decision some. Various problems unit associated with the formulation of bilayer tablets, such as layer-separation, low hardness, inaccurate individual layer weight management, cross-contamination between the layers, reduced yield etc. to beat these problems, development and production of quality bilayer tablets must be carried out.

Challenges in bilayer manufacturing

Conceptually, bilayer tablets are seen as a pair of single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

1. Cross-contamination: Any one layer granulation of intermixes with another layer granulation, cause cross-contamination.

2. Delamination: pill falls apart if the two halves of the pill do not bond completely. The two granulations have to be adhere once compressed.

3. Cost: Bilayer tableting is costlier than single-layer tableting for several reasons. First, the pill press costs. Second, the press generally runs lots of slowly in bilayer mode. Third, development of two compatible granulations is suggests longer time spent on formulation development, analysis and validation.

4. Production yields: to reduce cross contamination, dust collection & separation needed which results in losses. Further the whole process is slower, thus, bilayer tablets have lower yields than single-layer tablets.

Therefore, it's crucial to take care of all above challenges and necessary to urge associate insight into the root causes to allow design of a powerful product and methodology.

Advantages
* Smart physical and chemical stability
* Simple correct dosing and low content variability
* High level of patient acceptableness
* Competitive unit production prices
* Convenience of self-administration
* Easy to spot
* High convenience
* Straightforward to package and ship
Disadvantages
* Chance of disintegration and dissolution bioavailability
* May bother GI membrane (e.g. aspirin)
* swallowing Problem for; pediatric medicine and geriatrics
* IV or IM injections are simpler, in emergency cases.
* Some medication resist compression into tablets

Materials and methods

In current study, all the materials used were analytical grade material; the drug, Metformin Hydrochloride (MET-H) and Repaglinide (REPA) used were obtained from torrent research centre, Bhat, Gandhinagar, Gujarat.

The simultaneous estimation was carried for (MET-H) and (REPA) using UV spectrophotometer and as per developed method [(1)].

All elements including MET-H were passed screen 60# separately. In this study, polymers Polymer (Xanthan gum, Guar gum, HPMC K100 M, Eudragit-RSPO) were accurately weighed and mixed with MET-H, The mixture was granulated into RMG by slowly addition of 5 % PVP K 30 in isopropyl alcohol as granulating agent with microcrystalline cellulose at low speed until consistence mass obtained. The obtained granules were dried. The dried granules were passed through screen with mesh size 22. The obtained granules were evaluated with different pre-formulation tests. Same way for REPA, wet granules were prepared at trial and error with 5% PVP in IPA as binder and with Gum Acacia (GA), Acrypol -971and

HPMCK100M respectively. The prepared batches were evaluated for precompression and post compression evaluation parameter including assay and invitro drug release study.

The invitro dissolution test was performed in 0.1n HCl for 0-2 h and in pH-6.8 phosphate buffer for 2-12 h, in 900 ml dissolution media for 12 h at 37°C ± 0.5°C and paddle speed at 50 rpm. 5 ml dissolution media sample was withdrawn after every 1, 2, 4, 8 and 12 hours. The sink condition was maintained throughout study.

Kinetics of Drug Release and its Mechanism

A. Zero Order Release Rate Kinetics

The equation for zero order treatment is represented as

$$Qt = K0t$$

Where, Qt = amount of drug released in time (t) K0 = zero order release constant

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero order release kinetics, with a slope equal to K0.

B. First Order Kinetics

The equation for first order treatment is represented as

$$Log\ Q = Log\ Q0 – K1t /2.303$$

Where, Q = amount of drug remaining unreleased at time t

Q0 = initial amount of drug in solution

K1 = first order rate constant

The data plotted as cumulative percent drug retained versus time yields a straight line, it indicates that the release follows first order kinetics. The constant K1 can be obtained by multiplying 2.303 with slope values.

C. Higuchi Release Model [2, 3, 4]

The simplified Higuchi equation is represented as

$$Qt = KH\ t1/2$$

Where, Qt = amount of drug released in time t

KH = Higuchi's constant

A linear relationship between amount of drug released (Q) versus square root of time (t1/2) is observed if the drug release from the matrix is diffusion controlled.

D. Hixson-Crowell Model [6]

The simplified equations is represented as

$$Q01/3 - Qt\ 1/3= KHC.t$$

Where, Qt = amount of drug released in time (t) Q0 = initial amount of drug in solution KHC = cube–root constant

A graphic representation of cubic root of unreleased fraction of drug versus time will be linear if geometric shape of the formulation diminishes proportionally over time.

E. Korsmeyer and Peppas Release Model [7, 8]

The korsmeyer peppas model relates drug release exponentially to time. It is described by the following equation

$$Mt / M\infty = K\ tn$$

Where, Mt / M∞ = fractional release of drug

K = constant depending on structural and geometric characteristics of the drug dosage form

n = release exponent

The value of n indicates the drug release mechanism. This model is used to analyse the release of drug from polymeric dosage forms, when release mechanism is not understood or when there is a possibility of more than one type of release mechanisms are involved.

Table 1 Interpretation of Diffusion Release Mechanism from Polymeric Membrane

Release Exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion
0.5 < n < 1.0	Non - Fickian (Anomalous transport)
1.0	Case-II

Stability Study [9]

A stability study of optimized bilayer tablets (containing B3 & F10) was carried out by packing it in an airtight amber glass bottles. The bottles were kept at 40ºC ± 2ºC / 75% RH ± 5% RH tested at 6 month. The sample was then evaluated for stability by determining physical appearance, % drug content and invitro drug release.

RESULTS

The developed equations are shown here.

$$Cy = \frac{A_{\,299/283\ nm}}{A\ (1\%, 1cm)_{\ 299/283\ nm}\ \text{of RG}}$$

$$Cx = \frac{C_{Ax\ \ 208/232.4\ nm}}{A\ (1\%, 1cm)_{\ 208/232.4\ nm}\ \text{of MET} - H}$$

Where, A = Absorbance
A (1%,1cm) = Specific Absorptivity
Cx = MET-H Concentration (gm/100 ml)
Cy = RG Concentration (gm/100 ml)

$$C_{Ax\ \ 208/232.4\ nm} = A_{\ 208/232.4\ nm} - Ay_{208/232.4\ nm}$$

$$Ay_{208/232.4\ nm} = C_y \times A\ (1\%, 1cm)_{\ 208/232.4\ nm}\ \text{of RG}$$

As per **Absorption correction method** with standard addition, following formula obtained to determined drug concentration [Cx and Cy = Concentration of MET-H and RG respectively (gm/100 ml)]

For Estimation of drug in 0.1N HCL

Cy=absorbance at $\lambda 2_{(299)}$ /71.1944
Cx=[absorbance at $\lambda 1_{(208)}$-(Cy *678.417)]/91.1833
For Estimation of drug in Phosphate buffer pH 6.8
Cy=absorbance at $\lambda 2_{(283)}$ /78.77
Cx=[absorbance at $\lambda 1_{(232.4)}$-(Cy*678.417)]/113.93

The table no. 2 shows formulation for Batch F1-F10. While preparing MET-H layer, a second layer of SR polymer with dry binder was also formulated to mimic drug release condition of bilayer layer formulation. Pre-compression evaluation parameters for formulation F1-F10 for MET-H layer was carried out. Angle of repose; bulk density, tapped density, Hausner's ratio and Carr's index were obtained and all the batches obtain excellent –good flow properties. The Post compression determination viz. hardness, friability, uniformity of content, thickness and diameter estimated for bilayer tablet and assay was performed only for MET-H content. The friability was less than one while hardness was achieved as expected near 8 kg/cm^2; weight of bilayer tablet was near to theoretical weight 800 as it was in individual formulations.

Table 2 Composition of MET-H layer

Ingredients (mg)	MET-H Layer %									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
MET-H	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Xanthan gum	20	-	-	-	-	-	-	-	-	-
Guar gum	-	20	-	-	17.5	15	12.5	-	-	-
HPMCK100M	-	-	20	-	-	-	-	17.5	15	12.5
Eudragit RSPO	-	-	-	160	2.5	5	7.5	2.5	5	7.5
MCC	11	11	11	11	11	11	11	11	11	11
PVP K 30	5	5	5	5	5	5	5	5	5	5
Mg. Stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 3 Composition of REPA layer

Ingredients (mg)	RG Layer				
	F11	F12	F13	F14	F15
RG β-CD complex	4.66	4.66	4.66	4.66	4.66
Acacia gum	40	-	-	-	-
Acrypol -971	-	40	-	-	-
HPMCK100M	-	-	40	30	35
MCC	48.33	48.33	48.33	55	53.33
PVP	5	5	5	5	5
Mg. Stearate	1	1	1	1	1
Aerosil	0.5	0.5	0.5	0.5	0.5
Sunset Yellow	0.5	0.5	0.5	0.5	0.5

Table 3 indicates formulation composition for REPA layer. All the formulations F11-F15 were prepared in bilayer with second layer as selected MET-H layer. The calculated bulk density, tapped density, Hausner's ratio and % Carr's indicate that flow properties and

compressibility index were excellent –good flow character. The determinants viz. hardness, friability, uniformity of content, thickness and diameter estimated for bilayer tablet and assay was performed only for RG content. The hardness of all formulated tablets lies between 8.1 to 8.6 kg/cm^2. Friability was 0.4-0.31%. The weight variation and assay both were in control.

The invitro dissolution results are shown in figure 1 and figure 2 for both layer separately. All batches showed good control in release. Eudragit- RSPO showed highest control of drug release may be due to its hydrophobic nature against hydrophilic drug. The hydrophilic polymer and natural gum; HPMCK100M and guar gum respectively also showed good control over drug release but it was not sufficient to last till 12 hour. Further increase in concentration of them may give better control but rather than increasing their concentration

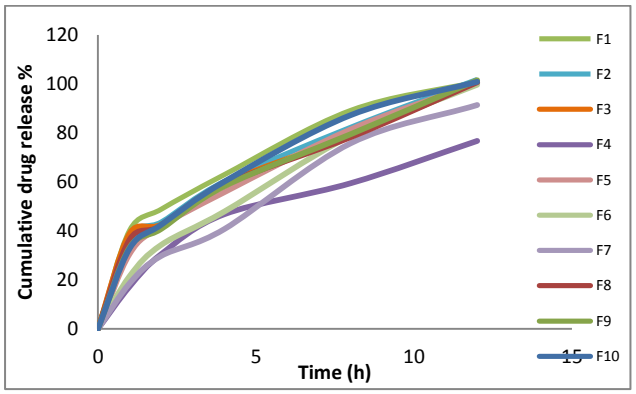

Figure 1 Invitro dissolution for MET-H

some part of them were replaced with hydrophobic polymer.

From results data of batch F1-F4, only batch F2, F3 were taken for further trial to modify drug release. Eudragit-RSPO, insoluble acrylic polymer was added gradually in increasing percentage starting with 2.5% replacing Guargum and HPMC K100 M from its 20%. Thus prepared formulation F5 to F10 showed decrease invitro drug release with increase in amount of Eudragit-RSPO. In F5-F10 no significance change in drug release among them was observed. Although there was more control of drug release than batch F26 containing HPMC alone. Among batch F5-F7, batch F6 and among batch F8-F10, batch F10 showed good initial drug release and sustain release till 12 hour.

For both selected batch, drug release profile were fitting to various kinetic models. Only data of 0-8 h were used for better consideration and data treatment was done in M. S. Excels. Table 4 shows kinetics for different model. In table R^2 indicates simple linear regression with its slop and 'r' indicates coefficient of correlations analysis.

Table 4 kinetic of drug release for F6 and F10

Sr. no.	Kinetic Model	Parameters	F6	F10
1	Zero order	R^2	0.9552	0.8990
		Slope	0.1173	0.1283
		correlation	**0.9967**	0.9481
2	First order	R^2	0.9881	0.9886
		Slope	-0.0034	-0.0017
		r	**-0.9917**	-0.9943
3	Higuchi	R^2	0.9845	0.9984
		Slope	4.1189	3.8875
		r	**0.9951**	0.9991
4	Hixon-Crowell	R^2	0.9552	0.899
		Slope	-0.0391	-0.0428
		r	**-0.9967**	-0.9481
5	Korsmeyer and Peppas	R^2	0.9971	0.9852
		Slope	0.6142	0.4734
		r	**0.9974**	0.9967
		n	0.61	0.47

The value of Korsmeyer and Peppas' coefficient (n) was 0.61 & 0.47 indicating anomalous and diffusion drug release for F6 and F 10 respectively. F6 was selected for second layer formation as it was near to zero order drug release form coefficient value.

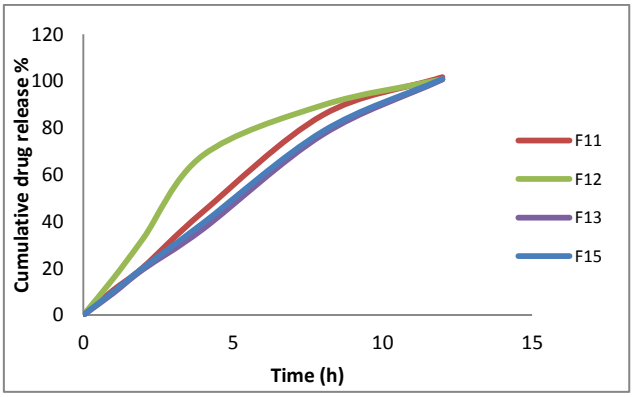

Figure 2 Invitro dissolution for REPA

Table 5 kinetic of drug release for F13 and F15

Sr. no.	Kinetic Model	Parameters	F13	F15
1	Zero order	R2	0.9993	0.9999
		Slope	0.1607	0.1627
		r	0.9995	1.0000
2	First order	R2	0.9617	0.9665
		Slope	0.0014	-0.0015
		r	0.9850	-0.9831
3	Higuchi	R2	0.8920	0.9013
		Slope	4.8026	4.8777
		r	0.9878	0.9494
4	Hixon-Crowell	R2	0.9993	0.9999
		Slope	0.0536	-0.0542
		r	0.9995	-1.0000
5	Korsmeyer and Peppas	R2	0.9757	0.7153
		Slope	0.9668	0.9891
		r	0.9995	0.9999
		n	0.9668	0.9891

Table 6 stability study results

	Before		After 6 month	
Physical Appearance	White -smooth surface		No change in color and texture	
Hardness	8.5±0.4		8.5±0.6	
Friability	0.25		0.27	
	MET-H	**REPA**	**MET-H**	**REPA**
Drug Content (%)	100.46	102.27	101.84	101.45
Time (min)	***Invitro* dissolution (%CDR)**			
0	0	0.00	0	0.00
1	21.47	9.97	22.47	9.29
2	34.28	20.23	35.86	19.63
4	47.92	39.3	48.62	38.94
8	78.96	78.52	79.27	79.63
12	99.72	100.93	100.62	102.34
Similarity index f_2	94.27 (for MET-H layer)		93.53 (For REPA layer)	

Form results it was observed that, F13 showed promising results and change in concentration of polymer was carried out to obtain minimum amount of polymer that give good results near to zero order drug F15, prepared in such way also gave good results as F13. Further both were compared based on release kinetics Shown in Table 5.

There was no significant difference between both batches and So F15 containing lesser amount of polymer was selected as final batch.

The results in table 6 indicate that there was no difference in selected formulation before and after stability period.

CONCLUSION

The bilayer tablets were successfully prepared for fixed dose combination drugs having both sustain release layer using wet granulation technique that release both drug up to 12 h and near to zero order drug release with stability.

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