INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION AND EVALUATION OF FLOATING TABLET OF ESOMEPRAZOLE MAGNESIUM DIHYDRATE

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ARTICLE INFO

Article history
Received 01/07/2017
Available online
30/07/2017

Keywords
Floating Tablets,
Chitosan,
HPMC K100M,
Direct Compression,
Buoyancy Studies.

ABSTRACT

Floating drug delivery system is the class of gastro retentive drug delivery systems. It is also called as Hydrodynamically balanced system. These are the low density systems they have the sufficient buoyancy to float over the gastric contents and remain buyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The aim of this work is to formulate and evaluate floating tablet of Esomeprazole Magnesium Dihydrate using the 3^2 factorial design. Chitosan and HPMC K100M is used as the independent variables. Sodium bicarbonate was used as the gas generating agent. Direct compression was the technique used for preparing the floating tablets. Esomeprazole Magnesium Dihydrate floating tablets were developed in nine different batches. The batches were evaluated for various physical parameters, floating lag time, floating time, swelling index, drug content and in-vitro dissolution profile. The floating lag time is between 150-30 seconds and the total floating time of the formulations not more than 9 hours. Drug release percentage of all the formulations is in between 88-94 % and kinetic studies were carried out and the best batch is F9. The best fit model is Korsemeyer's Peppas model.

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*Please cite this article in press as **Mr. Sachin G. Dhandore** et al. Formulation and Evaluation of Floating Tablet of Esomeprazole Magnesium Dihydrate. Indo American Journal of Pharmaceutical Research.2017:7(07).*

INTRODUCTION [1-4]:

Floating drug delivery system is designed to prolong the gastric residence time after the oral administration, at the particular site and controlling the release of drug. It is especially useful for achieving the controlled the plasma level as well as improving the bioavailability. In recent years scientific and technological advancements have been made in the research. Development of controlled release oral drug delivery systems by overcoming the physiological adversities like short gastric residence time and unpredictable gastric emptying time.

Floating drug delivery system has the less density (<1.004gm/cm^3) than gastric fluid that's why they remain buoyant in the gastric fluid and shows sustained release. This dosage forms will be very useful to deliver the narrow absorption window drugs which on oral administration prolongs it's gastric residence time there by increasing bioavailability, diminishing the side effects and enhanced patient compliance.

Esomeprazole Magnesium Dihydrate is an anti-ulcer agent. It has been reported the absolute bioavailability of Esomeprazole Magnesium Dihydrate when given orally is 50-60%. Biological half-life of Esomeprazole Magnesium Dihydrate is 1-1.5 hours and the main site of its absorption is upper part of the small intestine (proximal small intestine). A Hydrodynamically balanced system was planned for the Esomeprazole Magnesium Dihydrate as such a system when administered would remain buoyant on the gastric fluids for a prolonged period of time and drug would be available in the dissolved form at the main site of its absorption. In present research work Esomeprazole Magnesium Dihydrate is formulated as the gastro retentive drug dlivery system in the form of floatin tablets using polymers and other excipients in different ratios and then evaluated.

MATERIALS AND METHODS:

Materials

Esomeprazole Magnesium Dihydrate was procured from Cipla Pharmaceuticals Limited Kurkumb. Chitosan was procured from Colorcon Asia Pvt. Ltd. and HPMC K100M (Hydroxypropyl Methylcellulose), Carbapol 934P, Microcrystalline cellulose, Sodium bicarbonate, Magnesium stearate and Talc were procured from Loba Chemicals Mumbai.

Methods[5-7]:

Floating tablets of Esomeprazole Magnesium Dihydrate were prepared by direct compression technique. Sodium bicarbonate used as the gas generating agent so it's helpful for the Floating. All ingredients were accurately weighed and passed through the mesh 60# sieve. Then Except Magnesium stearate all other ingredients were blended uniformely in glass mortar, after sufficient mixing of drug as well as other ingredients ,Magnesium stearate was added as post lubricant and further mixed for additional 2-3 minutes. Pre-compressional parameter were carried out after that the tablets were compressed using Remek Mini press-I tablet machine. Weights of all the tablets were kept constant in all the formulations. As a part of preformulation studies, the λ-max of Esomeprazole Magnesium Dihydrate was determined by using UV-VIS Spectrophotometer (Shimadzu 1700) and the calibration curve of Esomeprazole Magnesium Dihydrate was designed by measuring absorbance at 300 nm in 0.1N HCl, making dilutions to yield concentration of 1-10 µg/ml. FTIR studies for the compatibility study of drug to polymers were performed for pure drug, polymers and formulation by using FTIR Spectrophotometer.

Table 1: Composition of floating tablet of Esomeprazole Magnesium Dihydrate (all the quantities in mg).

Sr no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Esomeprazole Mnagnesium Dihydrate	20	20	20	20	20	20	20	20	20
2	Chitosan	15	15	15	30	30	30	45	45	45
3	HPMC K100M	15	30	45	15	30	45	15	30	45
4	Carbopol 934P	20	20	20	20	20	20	20	20	20
5	MCC	95	80	65	80	65	50	65	50	35
6	Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
7	Magnesium Stearate	3	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2	2
9	Total	200	200	200	200	200	200	200	200	200

Evaluation Parameters[6,8-10]:

Pre-compression parameters

Angle of repose

Angle of repose has been used as indirect method to determine the flow property of the powder mixture. Angle of repose for powder mixture of each formulation was determined by fixed funnel method. In this method the funnel is secured with its tip with height 2cm, above a plane of paper kept on a flat horizontal surface. The powder were poured carefully through the funnel until the apex of conical pile so formed just reaches the tip of funnel. Angle of repose was determined by putting the values of the base radius 'r' and height of the pile 'h' in the given following equation.

$$\mathbf{Tan\theta = h/r}$$

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

Where, θ= angle of repose

h=height of pile and
r=radius of the pile

Table 2: Relationship between Angle of repose and Flowability.

Angle of Repose	Flowability
≤25	Excellent
25-30	Good
30-34	Acceptable
≥40	Very poor

Bulk Density

Bulk density was determined by pouring the accurately weighed quantity of precompressed powder into 25ml of graduated measuring cylinder. After that the bulk volume was noted down, this method was repeated for three times and the mean of the values were taken and final volume was calculated as a result of bulk volume. Bulk density of the powder mixture was determined by using the following formula:

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}}$$

Tapped Density

Tapped density was determined by pouring the accurately weighed quantity of precompressed powder into 25ml graduated measuring cylinder. Then the measuring cylinder was subjected to 100 tapping, this method was repeated for three times and the mean of the values were taken and the final volume was calculated as a result of tapped volume. Tapped density of powder mixture was determined by using following formula:

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}}$$

% Compressibility Index

Compressibility index is used to evaluate the flowability of precompressed powder by comparing the bulk density and tapped density of the powder mixture. The percent compressibility index of is direct measure of potential of powder properties arch or bridge strength is calculated by using the following formula:

$$\%\ CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Where, CI= Compressibility Index.

Table 3: Correlation between % Compressibility and Flowability.

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
≥40	Extremely Poor

Hausner's ratio

Hausner's ratio is also used to predict the flow properties of powder mixture. It provides an indication of the degree of densification which could result from vibration of feed hopper, interparticulate interaction and settling property can be measured by Hausner's ratio and it is calculated by using following formula:
Lower the Hausner's ratio better is the flow property.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 4: Hausner's ratio as an indication of powder flow.

Hausner's ratio	Flow property
≤1.18	Excellent
1.19-1.25	Good
1.3-1.5	Passable
≥1.5	Very poor

Post-compression parameters

The prepared floating tablets were evaluated fr quality control tests like weight variation, hardness, thickness, friability, content uniformity and In-vitro dissolution studies.

Diameter and Thickness

Three tablets from each batch of formulation were collected and diameter of tablets were measured with the help of electronic vernier caliper and the average diameter was calculated. Similarly thickness of tablet was also determined with the help of vernier caliper.

Weight Variation test

Weight variation test was performed as per IP 2007. Twenty tablets from each batch were taken and individually weighed using the electronic balance. Then the average weight (WA) was determined. The percent weight variation was calculated by using the following formula:

% Weight variation = (WA-WI) x 100/WA

Where, WA= Average weight of tablet
WI= Individual weight of tablet

Table 5: Tablet weight variation.

Weight	% Variation
Less than 80 mg	10%
80-250 mg	7.5%
Above 250 mg	5%

Tablet hardness

This test was carried out to check the whether the tablet have sufficient hard to resist breaking during the normal handling and transportation. The hardness of each batches of tablets were checked by using the Monsanto hardness tester. It was measured in Kg/cm^2.

Friability

Tablet hardness is not an absolute indicatore of strength of tablet. Friability generally refers to the loss in weight of tablets in the containers due to removal of fines from the tablet surface. The Roche friability test apparatus was used to determine the friability of the tablets. In this test twenty tablets from each batch were taken and weighed then placed in the friabilator, operated for 100 revolutions at 25 rpm for 4 minute and then tablets were removed from the friabilator and reweighed. The percentage friability was calculated by using the following formula:
If there is any chipping, capping, cracking or breaking of tablet the should be rejected.

$$\%F = (1 - W/W_0) \times 100$$

Where, W_0= weight of tablet before test
W=weight of tablet after test

Swelling index

Swelling of tablet due to the excipient particles involves the absorption of liquid resulting in an increase in weight and volume. In this test tablet of each batches were taken and weighed then placed in beaker containing 200ml of distilled water. Then after each hour the tablet was removed from the beaker and excess water from the surface was carefully soaked using filter paper and weighed this process is carried out upto 5 hours. The percent weight gain by the tablet was calculated by using the following formula:

$$\text{Swelling Index (S.I.)} = \{(Wt-Wo)/Wo\} \times 100$$

Where, S.I.=Swelling Index
Wt=weight of tablet at time t
W_0=weight of tablet before immersion

Drug content

In this test randomly selected three tablets of each batch, weighed and powdered all the tablets in glass mortar and pestle. Then average weight of three tablets were calculated. The quantity of powder equivalent to 100mg was transferred in a 100ml volumetric flask and diluted with distilled water to made 100 µg/ml concentration and filtered it. After that 1ml filtered solution diluted upto 100ml with distilled water to made concentration 10 µg/ml then the absorbance was measured at 300nm using the UV-Visible spectrophotometer. Each measurement was carried out three times and mean taken. The drug concentration was calculated from the standard calibration curve of drug.

In-vitro buoyancy studies

Buoyancy studies of the prepared floating tablets were carried out by visual observation. In this buoyancy test the prepared tablets were placed in beaker containing 100ml 0.1N HCl (pH1.2, temp. 37±0.5^{0}C) time taken for the tablet to emerge on the surface of the medium and this time taken as a Floating Lag Time (FLT). Total duration of time by which tablet remain buoyant on the surface of the medium is called as Total Floating Time (TFT).

In-vitro Dissolution studies

Dissolution studies of all the formulation batches (F1-F9) were carried out in dissolution test apparatus (USP Type-II). The dissolution test performed in 900ml of dissolution media 0.1N HCl pH1.2 for 9 hours at 50 rpm at 37±0.5^{0}C. 2ml of sample solution withdrawn at different time intervals (0,0.25,0.5,1,2,3,4,5,6,7,8 and 9 hours) and then filtered. After that 1ml of filtered sample solution further diluted upto 10ml with the same dissolution media 0.1N HCl pH1.2 and analyzed for the drug content by using the UV-Visible spectrophotometer (Shimadzu-1700) at 300nm. Before that 2ml sample was replaced in the vessel after each withdrawal for maintaining sink condition. From the in-vitro dissolution studies percentage drug release was calculated then the percentage drug release plotted against the time to study the release pattern of the drug. The kinetic models used were zero order, first order, Higuchi and Korsemeyer's-Peppas model. The model fit was evaluated using the correlation coefficient values (R^2).

RESULTS AND DISCUSSION

Pre-compression parameters

Angle of repose (θ):

The values obtained for angle of repose of formulation batches (F1-F9) were given in the table 6. The values were found to be in the range in between 25.41-28.73 so it indicates that the good flow property of the powder blend or mixture for the direct compression method.

Compressibility index:

The values obtained for Compressibility index for all formulation batches (F1-F9) were given in the table 6. Compressibility index values ranges in between 17.05-19.88 %, it indicates that the powder mixture have the required flow property.

Table 6: Preformulation Parameter of Powder Mixture.

Formulation	Angle of Repose	Loose Bulk Density (gm/ml)	Tapped Bulk Density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	27.61±0.584	0.572±0.049	0.714±0.022	19.88±0.024	1.24±0.026
F2	25.62±0.605	0.546±0.028	0.665±0.011	17.89±0.055	1.21±0.048
F3	26.78±0.574	0.539±0.039	0.679±0.015	20.61±0.046	1.25±0.047
F4	25.89±0.681	0.529±0.019	0.658±0.021	19.60±0.015	1.24±0.026
F5	26.68±0.721	0.580±0.015	0.703±0.036	17.49±0.047	1.21±0.076
F6	28.73±0.542	0.496±0.041	0.605±0.045	18.01±0.017	1.21±0.036
F7	27.89±0.475	0.512±0.034	0.645±0.055	20.62±0.027	1.25±0.055
F8	25.41±0.534	0.543±0.051	0.665±0.042	18.34±0.032	1.22±0.062
F9	27.28±0.458	0.569±0.039	0.686±0.049	17.05±0.015	1.20±0.025

Post-compression parameters

Tablet dimensions:

The dimensions of all the formulation batches (F1-F9) of floating tablets were determined and tabulated in the table 7. The mean thickness of tablets were uniform in all formulation batches and were found in the range between 3.41-3.42 mm, where as the diameter of tablets ranges in between 8.71-8.72 mm respectively.

Hardness test:

The hardness of prepared tablets were measured and given in the table 7. The hardness of tablets ranges in between 3.03-4.3 kg/cm^2.

Friability test:

The friability test were carried out using Roche Friabilator machine and all data were shown in the table 7. The % friability was less than 1% in all the formulation batches it indicates tablets were mechanically stable.

Table 7:Post-compression Parameters of Batches (F1-F9).

Sr No.	Batches	Tablet Dimensions		Hardness (kg/cm2) Mean ±SD n=3	Friability (%)
		Diameter(mm) Mean ±SD n=3	Thickness(mm) Mean ±SD n=3		
1	F1	8.72±0.010	3.41±0.011	3.03±0.04	0.63±0.017
2	F2	8.71±0.015	3.42±0.010	3.53±0.04	0.61±0.02
3	F3	8.71±0.015	3.42±0.015	4.03±0.04	0.65±0.015
4	F4	8.72±0.010	3.41±0.011	3.96±0.41	0.62±0.011
5	F5	8.72±0.011	3.42±0.010	3.66±0.20	0.58±0.015
6	F6	8.72±0.015	3.42±0.011	4.0±0.19	0.63±0.011
7	F7	8.71±0.011	3.42±0.011	4.3±0.28	0.61±0.015
8	F8	8.71±0.015	3.42±0.015	3.96±0.40	0.63±0.017
9	F9	8.72±0.01	3.42±0.011	4.2±0.19	0.65±0.011

Weight variation test:

Weight variation test is important parameter for the tablet formulation. Weight variation test was done by using 20 tablets of each batches by comparing individual weight of tablets with the average weight of tablet and all the data obtained were given in the table 8.

Buoyancy study:

Buoyancy study is one of the important parameter for the floating tablets. Buoyancy study was carried out in 0.1N HCl (pH 1.2) at 37±0.5^{0}C and the results of the buoyancy studies were given in the table 8.

Table 8:Post-compression Parameters of Batches (F1-F9).

Sr No.	Batches	Weight Variation test (g)	Buoyancy Studies		Drug Contents (%)
			Floating lag time (Sec)	Total floating time (Hrs)	
1	F1	0.200±0.006	150	>8	94.20
2	F2	0.199±0.005	112	>9	97.38
3	F3	0.201±0.008	80	>9	96.70
4	F4	0.205±0.006	62	>9	97.04
5	F5	.0200±0.005	45	>9	98.15
6	F6	0.199±0.008	38	>9	97.29
7	F7	0.197±0.005	30	>9	96.31
8	F8	0.201±0.006	30	>9	98.30
9	F9	0.199±0.007	30	>9	97.54

Swellimg study:

Due to hydrophilicity of the polymer it absorbs the water so tablet get swells. As the result swelling increases as the time passes because of the hyrophilicity the polymer and determined values were given in the table 9.

Table 8: Swelling Index of Batches (F1-F9).

Sr.No	Time (Hrs)	Swelling Index (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	36.96	53.52	60.55	57.89	55.80	53.65	57.23	54.35	55.76
2	2	64.21	68.38	77.41	72.51	67.35	66.36	67.41	65.63	66.35
3	3	70.83	74.7	80.35	75.43	76.45	72.51	73.38	73.58	72.84
4	4	73.49	78.08	84.75	81.28	83.52	84.75	83.56	82.86	83.53
5	5	84.09	86.76	92.08	88.59	90.50	92.15	91.23	90.54	92.35

In-vitro dissolution study:

Dissolution studies were carried out in dissolution test apparatus (USP Type II) using 0.1N HCl (pH1.2) as a dissolution media. The tablet swelled during the dissolution study and remained as buoyant for more than 9 hours. So due to this dissolution study carried out for 9 hours, it was found that F9 batch shows the better sustained release characteristics and better floating lag time 30 sec. All in-vitro dissolution studies data shown in the table 10.

Table 10: % cumulative drug release of F1-F9 batch.

Time in Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.25	15.03	11.74	9.54	13.93	9.54	8.45	9.54	9.54	6.25
0.5	20.54	19.43	16.14	18.34	18.33	9.55	17.24	12.85	10.65
1	30.42	28.22	24.93	27.13	28.22	17.24	27.12	19.44	16.14
2	40.31	38.11	34.82	37.01	38.11	26.03	35.92	29.32	26.03
3	50.20	49.10	45.80	48.00	49.10	35.91	45.80	38.11	35.91
4	57.89	56.79	53.50	55.69	56.79	45.80	53.50	48.00	45.80
5	66.68	65.58	62.29	64.48	64.48	55.69	63.38	56.79	55.69
6	75.47	76.57	72.17	74.37	75.47	65.58	72.18	66.68	65.58
7	82.07	82.07	78.77	80.97	82.07	74.37	82.06	75.47	75.47
8	88.66	89.76	87.56	89.76	85.37	80.97	87.56	84.26	85.36
9	94.15	91.96	90.86	93.06	91.96	90.85	89.76	91.95	88.66

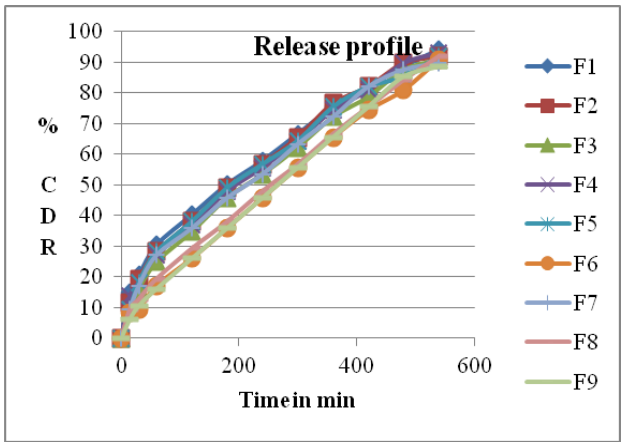

Figure 1: In-vitro dissolution drug release of F1-F9 batch.

Release kinetics:

After dissolution study formulation batches (F1-F9) further studied for the release kinetic most of the batches fit to Higuchi model, Korsemeyer's Peppas model and Zero order. Korsemeyer's-Peppas model best fit to F9 batch.

Table 11: Kinetic release data of different model for optimized batch F9.

Model	R^2 Value
Zero order	0.9938
1st order	0.9529
Higuchi matrix	0.9635
Korsemeyer's Peppas	0.9977

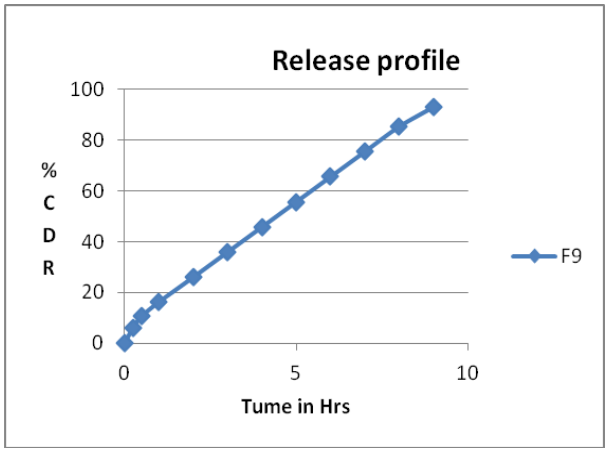

Figure 2: In-vitro dissolution release of F9 batch.

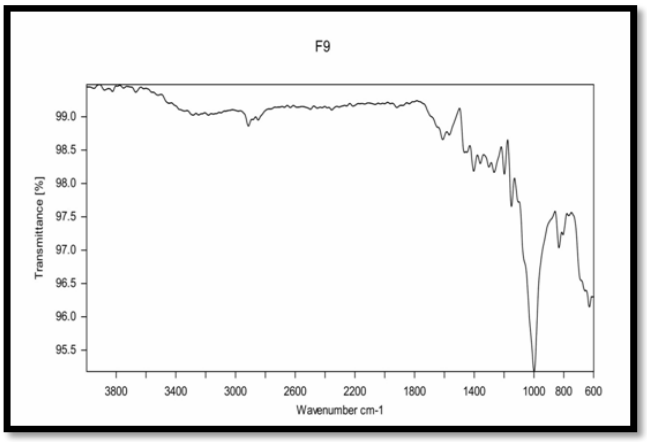

Figure 3: IR Spectrum of Optimized F9 Batch.

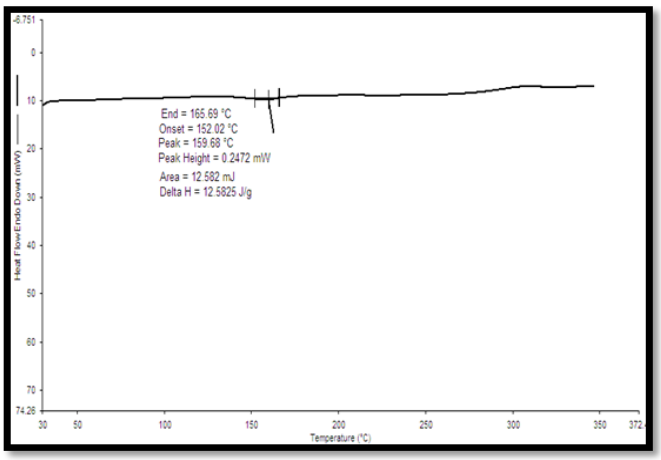

Figure 4: DSC Thermogram of Optimized F9 Batch.

CONCLUSION

From the study we can concluded that the amount of Chitosan and amount of HPMC K100M had significant effect on drug release rate, floating lag time and total floating time.

F9 Batch gave the better sustained release of drug and better floating lag time so this batch selected as the best formulation batch.

Kinetic release study shows the release mechanism of the drug fitted to Korsemeyer's Peppas model.

ACKNOWLEDGEMENT

The authors thank the SVPM's college of Pharmacy for providing the facilities and encouragement and also thanks the Cipla Pvt. Ltd. Kurkumb for providing the drug as a gift sample.

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