The Pharmaceutical and Chemical Journal, 2022, 9(3):150-159

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Design, Characterization and Evaluation of Floating Microencapsules of Ilaprazole by Hot Melt Granulation Method

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Abstract Microencapsulation is described as a process of enclosing micron-sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment. Hot-melt granulation (HMG) has gained interest in the pharmaceutical field as a processing technology capable of producing solid dispersions with a high degree of drug-polymer interactions. The simultaneous mechanical and thermal shear of samples achieved by HMG can noticeably modify drug properties such as solubility, poor taste, and flow-ability, while producing sustained drug delivery systems. In Hot Melt Granulation Amount of meltable binder is 10%-30% w/w with respect to that of fine solid particles is used. A Meltable binder suitable for melt a granulation has a melting point typically within the range of 60-80 °C. Hydrophilic Meltable binders are used for preparation of immediate-release dosage forms while the hydrophobic Meltable binders are preferred for prolonged-release formulations. The current work elaborates the mechanism of hot melt granulation over traditional method for sustained release of drug and long lasting effect. In the present study stearic acid, Glyceryl monosterate, Cetyl alcohol were used as base and various polymers like HPMC K100 M, Guargum, Xanthum gum, were used in various concentrations. From this formulations HPMC K100 M in the concentration of 2% (I12) gives sustain drug release as 100.76% for 12 hrs and follows zero order kinetics. Where other polymers *i.e.* Xanthum gum Guargum, were not able to retain the drug release for 12 hrs in various concentrations.

Keywords Microencapsulation, Hot melt Granulation, Stearic acid, Glyceryl monosterate, Cetyl alcohol, HPMC K100 M

Introduction

Microencapsulation is a technique by which solid, liquid or gaseous active ingredients are packaged within a second material for the purpose of shielding the active ingredient from the surrounding environment. Thus the active ingredient is designated as the core material whereas the surrounding material forms the shell. This technique has been employed in a diverse range of fields from chemicals and pharmaceuticals to cosmetics and printing. For this reason, widespread interest has developed in microencapsulation technology [1]. HME technology offers some distinct advantages over traditional methods of encapsulation. Notably, HME is generally a solvent free (or minimal amount of solvent) technique, is cost efficient, entails a small equipment "footprint," is a continuous (melting, mixing, and shaping) process, and is suitable for numerous matrix materials and encapsulants [2]. Most microcapsules have diameters between a few micrometers and a few millimeters [3]. The controlled drug delivery system has used to reduce the problems associated with conventional therapy and to improve the therapeutic

efficacy of a given drug. Microencapsulation is the enveloping of liquid droplets or fine solid particles to form microcapsule, having an average diameter as small as 1 μm to several hundred micrometers. Microencapsulation of materials is resorted to ensure that the encapsulated material reaches the area of action without getting adversely affected by the environment through which it passes [1]. Microcapsules can be classified on the basis of their size or morphology into mononuclear, polynuclear and matrix types. Generally the choice of the microencapsulation method depends on the nature of the polymeric/monomeric material used. Thus appropriate combination of starting materials and synthesis methods can be chosen to produce microencapsulated products with a wide variety of compositional and morphological characteristics. For preparation of microencapsules one can use physical methods or chemical methods.

A. Physical Methods

a) Spray Drying
b) Spray Chilling
c) Fluid Bed Coating
d) Multi-orifice Centrifugal Process
e) Pan Coating
f) Air Suspension Coating
g) Centrifugal Extrusion

B. Chemical Methods

a) Coacervation Phase Separation
b) Solvent evaporation
c) Solvent Extraction
d) Interfacial Polymerization
e) In-Situ Polymerization
f) Matrix polymerization

Table 1: Different techniques used for microencapsulation

Sr no	Chemical processes	Physico-chemical processes	Physico-mechanical process
1	Interfacial Polymerization	Coacervation and phase separation	Spray drying and Congealing
2	In situ polymerization	Sol-gel encapsulation	Fluid bed coating
3	Poly condensation	Supercritical CO_2 assisted microencapsulation	Pan coating Solvent evaporation

Table 2: Microencapsulation processes and their applicability

Sr No	Microencapsulation process	Nature of the core material	Approximate particle size (mm)
1	Air suspension	Solids	5–5000*
2	Coacervation and phase separation	Solids and liquids	2–5000*
3	Multi-orifice centrifugation pan coating	Solids and liquids	1–5000*
4	Spray drying and congealing	Solids	600–5000*
5	Solvent evaporation	Solids and liquids	600
		Solids and liquids	5–5000*

*The 5000 mm size is not a particle size limitation. The methods are also applicable for macrocoating.[6]

Hot Melt granulation

Microencapsualtion is highly used as it increases the stability and life of the product. It retards evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack [3]. In Hot melt granulation there is a use of binders which merges the active pharmaceutical ingredients and other excipients of the dosage form. The binders used in (HMG) has relatively low melting point about 60^0C. Granulation is nothing but the process of forming or crystallizing into grains. Granules may vary in their size between 0.2 and 4.0 µm depending on their way of usage in dosage form. Granulated substance has to be mixed with other excipients before tablet compression or capsule filling. Melt granulation is a single step technique converting fine powders into granules of various sizes and more or less regular spherical shape [4]. Hot melt Granulation is an excellent method for drugs which has poor solubility. The risk of dissolving the drug during the process is very least. Hot melt extrusion method is continuously getting into the limelight as there is a continuous increase in poor soluble compounds in pharmaceutical industry. The method not just increase the solubility but the bioavailability of drug too. The technology (HMG) has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in the pharmaceutical industry [5-6]. This method is also very easy to scale up on industrial level. The Hot Melt Extrusion process makes it possible to convert a mix of raw materials into a product with specific characteristics, such as uniform shape and density, by forcing the mix through a die under controlled conditions. For this, HME exploits a molten system, the viscosity of which must be controlled to enable the flow through the die. HME is a continuous process where heat and pressure are applied to melt or soften materials through an orifice to produce new products of uniform shape and density. The extrusion process can change the physical properties of a substance when it is being forced through an orifice or die on the hot-melt extruder under controlled conditions. The main component of HME is the extruder. Some of the basic elements that are assembled to make an extruder include a motor, an extrusion barrel, rotating screws in the barrel and a die or orifice that is connected at the end of the extruder.

Advantages

1. To protect the sensitive substances from the external environment.
2. To mask the organoleptic properties like colour, taste, odour of the substance.
3. To obtain controlled release of the drug substance.
4. For safe handling of the toxic materials.
5. To get targeted release of the drug.
6. To avoid adverse effects like gastric irritation of the drug, e.g. aspirin is the first drugwhich is used to avoid gastric irritation [7].

Requirements of Hot Melt Granulation

Amount of meltable binder is 10%-30% w/w with respect to that of fine solid particles isused. A Meltable binder suitable for melt a granulation has a melting point typically within the range of 60-80°C. Hydrophilic Meltable binders are used for prepare immediate-release dosage forms while the hydrophobic Meltable binders are preferred for prolonged-release formulations. The melting point of other fine solid particles should be at least 20°C more thanthat of the maximum processing temperature [8, 9].

2. Material and Method

2.1 Materials

Drug- Ilaprazole

Polymers and Excipients-Stearic acid, Glyceryl monosterate, Cetyl alcohol, HPMC K100 M, Xanthum gum, Gaurgum, Sodium Bicarbonate, Lactose and Aerosil.

2.2 Method

Stearic acid, Glyceryl monosterate, Cetyl alcohol were alone or in combination was dissolve at 60-70^{0}C in Petri dish then required amount of polymer like HPMC K100 M, Xanthum gum, Gaurgum, was added to it then sodium bicarbonate was addedto it then Lactose and Aerosil were added to it then finally drug was added and it was cool to form a congeal mass then this was passed through sieve no 100 and was dried and then evaluation tests were performed.

Table 3: Formulation of Floating Microencapsulation of Ilaprazole

Ingredients	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
Cetyl alcohol (mg)	250	-	500	-	-	-	500	-	-	500	500	-
Glyceryl monosterate(mg)	-	500	-	500	500	500	-	500	500	-	-	-
Steric acid (mg)	-	-	-	-	-	-	-	-	-	-	-	500
HPMC	-	-	1%	1%	-	-	-	1.5%	2%	1.5%	2%	2%
Xanthan Gum	-	-	-	-	1%	-	-	-	-	-	-	-
Gaurgum	1%	1%	1%	1%	1%	1.5%	1.5%	1%	1%	1%	1%	1%
Ilaprazole (mg)	10	10	10	10	10	10	10	10	10	10	10	10
Sodium Bicarbonate(mg)	150	150	150	150	150	150	150	150	150	150	150	150
Lactose (mg)	50	50	50	50	50	50	50	50	50	50	50	50
MCC (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Dose (mg)	250	250	230	400	250	400	385	450	450	375	500	400

3. Evaluation Parameters [10-15]

3.1 Determination of λ_{max}

The standard solutions of Ilaprazole were scanned in the range of 200-400 nm against 0.1N HCl solution as a blank. Ilaprazole showed maximum absorbance at 305 nm.

→ Calibration curve of Ilaprazole in 0.1N HCl buffer

Preparation of standard stock solution: A standard stock solution containing 1000µg/ml was prepared by dissolving 100 mg of Ilaprazole in100 ml of 0.1N. HCl solution.

Preparation of the test solution

Ilaprazole The standard stock solution containing 1000µg/ml of Ilaprazole, was prepared in 0.1 N HCl, from this stock solution pipette out and dilutions were prepared as 5,10,15,20,25 µg/ml and absorbance was taken at 305 nm.

3.2 Preformulation Studies

In the preformulation studies Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose, were performed.

3.3 Particle size determination

Particle size determination was performed by optical microscopy method. First stage and eye piece micrometer were taken then microscope was calibrated using stage and eyepiece micrometer. Then the solution of microencapsules was prepared then it was spread on slide as a thin film and was observed under this microscope and particle size was detected.

3.4 Floating lag time- In this test 100 mg of Floating Microencapsules was added into the 900 ml dissolution vessel containing 0.1N HCl at 37 °C. It is the time the formulation took to emerge on surface of dissolution medium is referred as floating lag time.

3.5 Floating duration- In this test 100 mg of Floating Microencapsules was added into the 900 ml dissolution vessel containing 0.1N HCl at 37 °C. The time that formulation took to remain constantly floating on surface of dissolution medium is referred as duration of floating.

3.6 Percentage Drug Entrapment Efficacy (%DEE)

The yield of microencapsules were determined by comparing the whole weight of Microencapsules formed against the combined weight of the copolymer and drug.

$$\%Practicle\ yield = \frac{Massof\ microencapsules\ obtained}{Total\ weight\ of\ drug\ and\ polymer\ used} \times 100$$

3.7 Drug Content Uniformity

Accurately weighed microencapsules equivalent to 100 mg were suspended in 100 ml of 0.1 N HCl, it was shake for 30 min and kept for 24hrs. Next day it was stirred for 5 min and filtered. After suitable dissolution, the drug content in the filtrate was analyzed spectro photo metrically at using Shimadzu UV spectrophotometer.

The drug content uniformity was calculated by.

$$\text{Percentage Drug Entrapment Efficiency} = \frac{Actual\ Drug\ Content}{Theoretical\ drug\ Content} \times 100$$

3.8 Filled capsules parameter

a. Capsule appearance: The prepared capsule was evaluated visually.

b. Capsule lock length: The capsules lock length was determined using Vernier caliper. Six capsules from each batch of formulation were used and mean lock length value and stand.

c. Weight variation: To study the weight variation, 20 capsules of each formulation were weighed using an electronic digital balance. The average weight of each capsule was calculated and the percentage deviation in weight was calculated.

3.9 *In vitro* dissolution study-An *in vitro* release study was carried out using dissolution test apparatus USP Type II (Paddle Method). Dissolution parameters used for the study are as given in table 4.

Table 4: Parameters used in *in vitro* dissolution study

Dissolution medium	**900 ml of Hydrochloric acid buffer solution of pH 1.2**
Temperature	37 °C ± 0.2 °C
Speed of rotation (RPM)	50

3.2 Drug Kinetic study

The release data obtained from various batches were studied with respect to effect of drug: polymer ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of optimized batches was fitted to zero order, first-order, Higuchi, Hixson- Crowell, Korsemeyer and Peppas models to ascertain the kinetic modeling of drug release.

4. Result and Discussion

4.1 Calibration curve of Ilaprazole in 0.1 N Hydrochloric Acid

100 of drug Ilaprazole was dissolved in 0.1 N Hydrochloric Acid Buffer and volume was makeup to 100 ml. And dilutions were made as 5, 10, 15, 20, 25 µg/ml and absorbance was taken at 305nm. It is given in table 5.

Table 5: Calibration curve of Ilaprazole 0.1 N Hydrochloric Acid

Sr. No	Concentration (ug/ml)	Absorbance
1.	0	0
2.	5	0.232
3.	10	0.406
4.	15	0.578
5.	20	0.756
6.	25	0.912

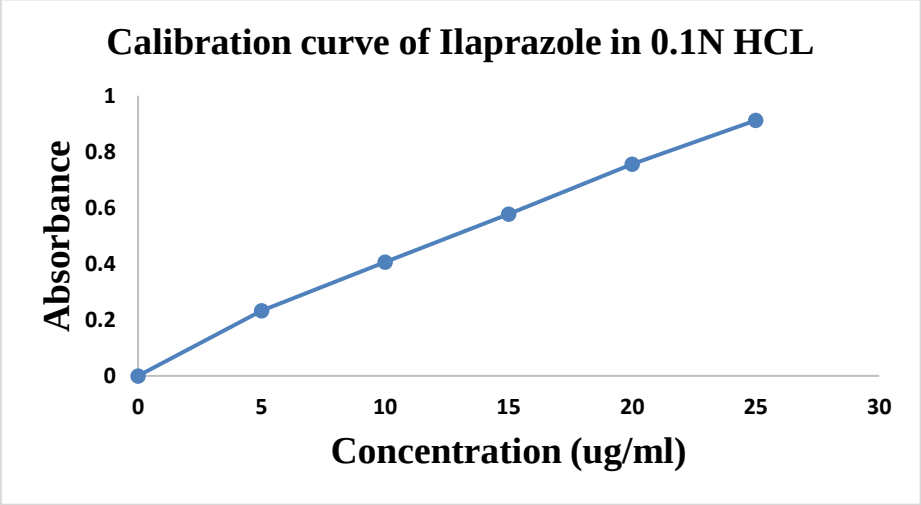

Figure 1: Calibration curve of Ilaprazole in 0.1 N Hydrochloric Acid

4.2 Preformulation Studies

All the preformulation studies like bulk density, tap density, angle of repose etc, physical characterization of drug sample, Analytical characterization of drug sample were performed.

Table 6: Preformulation testing (g= gram)

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	(%) Compressibility	Hausner Ratio	Angle of Repose (θ)
I1	0.505 ±0.12	0.6733 ±0.31	24.99 ±0.34	1.23 ±0.21	33.53^o $\pm 0.43^0$
I2	0.666 ±0.24	0.833 ±0.11	20.00 ±0.32	1.25 ±0.25	32.27^o $\pm 0.34^0$
I3	0.712 ±0.21	0.901 ±0.34	20.97 ±0.25	1.26 ±0.22	35^o $\pm 0.33^0$
I4	0.756 ±0.14	0.875 ±0.18	13.60 ±0.30	1.15 ±0.11	34.30^o $\pm 0.19^0$
I5	0.5205 ±0.095	0.6826 ±0.231	23.75 ±0.14	1.21 ±0.23	34.78^o $\pm 0.15^0$
I6	0.6545 ±0.13	0.7882 ±0.33	16.96 ±0.21	1.2 ±0.34	32.57^o $\pm 0.13^0$
I7	0.677 ±0.20	0.8002 ±0.38	15.4 ±0.19	1.18 ±0.14	35.05^o $\pm 0.24^0$
I8	0.632 ±0.102	0.765 ±0.30	17.39 ±0.32	1.21 ±0.16	33.89^o $\pm 0.23^0$
I9	0.54 ±0.21	0.62 ±0.29	11.96 ±0.17	1.14 ±0.17	26.57 $\pm 0.33^0$
I10	0.62 ± 0.23	0.69 ±0.27	11.11 ±0.33	1.13 ±0.22	27.51 $\pm 20^0$
I11	0.57 ±0.098	0.63 ±0.19	9.71 ±0.25	1.11 ±0.16	29.05 $\pm 0.21^0$
I12	0.65 ± 0.13	0.71 ±0.17	9.68 ±0.29	1.11 ±0.20	28.52 $\pm 0.26^0$

N=3

The results of the bulk density and tapped density were mentioned in an above table. The bulk density and tapped density values were lies in between 0.505 ±0.12 to 0.756 ±0.14 g/cm^3 and 0.673 ±0.31 to 0.901±0.34 g/cm^3 i.e. less than 1.2, indicates good packing. The values of % compressibility, Hausner ratio and angle of repose were lies in between 13.60% ±0.30% to 24.99% 0.34%, 1.11 ±0.11 to 1.26 0.12 and 26.57 ±0.33 to 35.05 ±0.33, respectively indicates acceptable flow property and also good packing ability.

4.3 Particle size determination

The size of microencapsules was obtained by Optical microscopy using Stage and eyepiece microscope. The size was found to be 0.149 ± 0.016 mm. for optimized batch.

Table 7: Various Characterization of floating microencapsules of Ilaprazole

Formulation code	%DEE	Drug content Uniformity (%)	Floating lag time (Sec)	Floating Time (Hr)
I1	86	60	Immediate	>12
I2	84	70	Immediate	>12
I3	85	65	Immediate	>12
I4	89	70	Immediate	>12
I5	86	72	Immediate	>12
I6	85	78	Immediate	>12
I7	83	80	Immediate	>12
I8	89	84	Immediate	>12
I9	91	60	Immediate	>12
I10	94	70	Immediate	>12
I11	92	65	Immediate	>12
I12	99	70	Immediate	>12

4.4 % Drug Entrapment Efficiency (%DEE): The yield of microencapusles weredetermined by comparing the whole weight of beads formed against the combined weight of the copolymer and drug. %DEE of formulated microencapsules was found to be 90 to99%. The optimized batch I12 gives %DEE as 99%.

- **Drug Content Uniformity:** All the prepared formulations show drug content uniformity in the range of 60-84%. The optimized batch I12 show drug content uniformity 70%.
- **Floating Lag time:** Floating lag time of all the prepared formulations was observed by visual examination. All the prepared formulations show Floating lag time to immediate. And the optimized batch I12 show immediate floating after entering in 0.1 N HCl and show floating for more than 12 hrs.
- **Floating Duration:** All prepared formulation show floating duration more than 12 hours.

4.5 Evaluation of Filled Capsule

- Physical Description
- Colour: White
- Weight of empty capsule :65±3 mg

Table 8: Other Evaluation parameters of Floating microecapsules Ilaprazole

Parameters	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
Capsule Lock Length	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6
Weight Variation	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes

Capsules of different formulations were subjected to various evaluation tests, such as capsule lock length, uniformity of weight, drug content. All formulations showed uniform capsule lock length. The weight variation test was carried out as per official method and the per cent deviation of formulation was found to be within limit.

4.6 *In vitro* dissolution study- An in vitro release study was carried out using dissolution test apparatus USP Type II (Paddle Method).

Table 9: % Drug release of Miceoencapsules of Ilaprzole

Time	% Drug Release											
(hr)	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	32.99	4.34	85.14	40.46	15.68	3.12	18.05	3.12	35.48	52.90	42.95	3.12
2	45.47	8.09	92.76	70.37	25.54	5.61	33.01	5.61	40.50	60.43	55.44	5.61
3	57.97	20.51	95.77	75.39	33.03	8.11	35.54	18.06	90.33	72.95	70.44	18.06
4	75.46	28.04	-	79.93	48.01	13.09	40.55	28.04	95.41	85.47	82.96	28.04
5	87.99	38.03	-	84	55.53	20.58	-	38.03	-	-	88.03	38.03
6	-	45.45	-	86.24	65.55	25.58	-	48.03	-	-	-	48.03
7	-	-	-	88.57	-	-	-	55.55	-	-	-	55.55
8	-	-	-	90	-	-	-	63.08	-	-	-	66.08
9	-	-	-	92.54	-	-	-	70.62	-	-	-	70.62
10	-	-	-	93.88	-	-	-	80.65	-	-	-	80.65
11	-	-	-	-	-	-	-	-	-	-	-	90.70
12	-	-	-	-	-	-	-	-	-	-	-	100.76

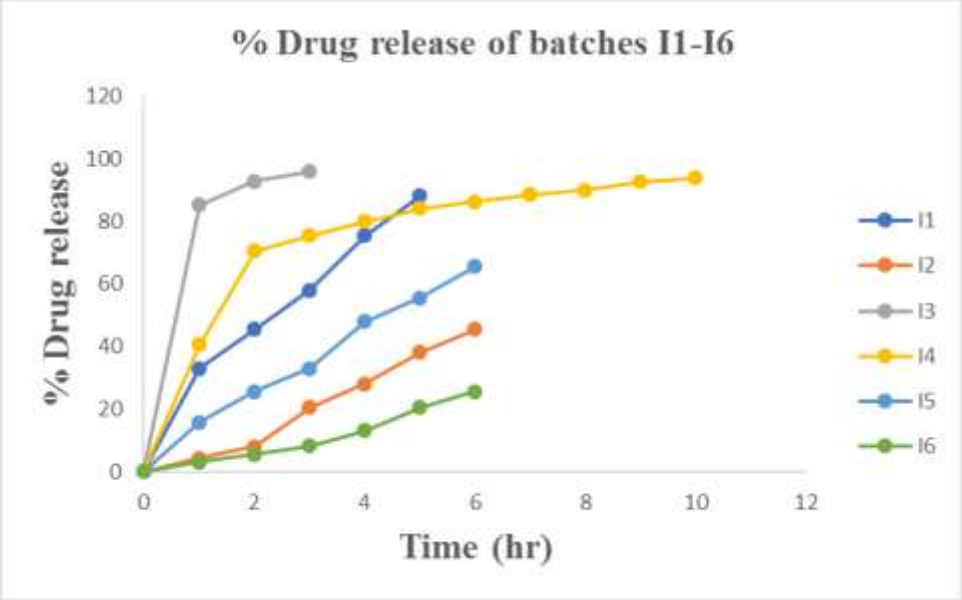

Figure 2: % Drug release of batches I1-16

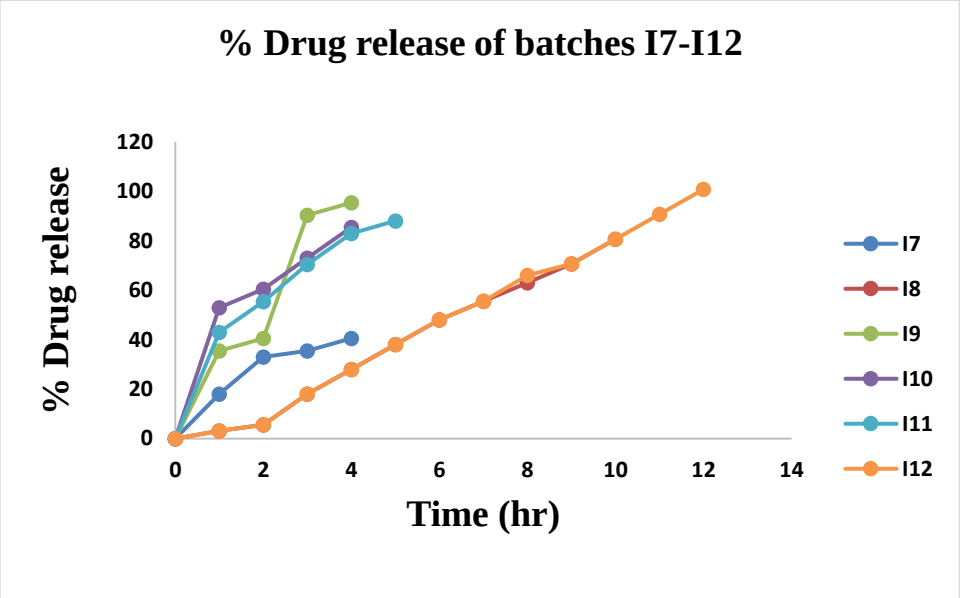

Figure 3: % Drug release of batches I7-I12

4.7 Kinetic Studies

The release data obtained from various batches was studied with respect to effect of drug: polymer ratio, diluents ratio. Dissolution data of drug from prepared in situ gel at different time periods was plotted as cumulative % drug release v/s time. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. It was found that the optimized batch I12 follow Zero order model. The drug release kinetics from all the batches were calculated, which was illustrated as follows.

Table 10: Kinetic study of Floating Microencapsules of Ilaprazole

Batch	Zero order	First order	Matrix	Peppas	Hixon crowell	Best model fit
I1	0.9692	0.9726	0.9874	0.9905	0.9900	Peppas
I2	0.9568	0.9509	0.8349	-	0.9538	Zero order
I3	0.6921	-	0.9216	0.9897	0.6848	Peppas
I4	0.9153	-	0.9941	0.9928	0.9667	Matrix
I5	0.9935	0.9905	0.9598	0.9950	0.9959	Hixon crowell
I6	0.9714	0.9601	0.8600	0.9836	0.9641	Peppas
I7	0.9177	0.9458	0.9900	0.9644	0.9372	Matrix
I8	0.9894	0.9470	0.8874	0.9870	0.9683	Zero order
I9	0.9650	0.9305	0.9362	0.9122	0.9516	Zero order
I10	0.8636	0.9769	0.9886	0.9696	0.9556	Matrix
I11	0.9000	0.9955	0.9981	0.9945	0.9836	Matrix
I12	0.9921	-	0.8907	0.9880	0.8043	**Zero order**

Optimisation

In the present study *i.e.* formulation and evaluation of floating microencapsulation of Ilaprazole various polymers like HPMC K100 M, Guargum, Xanthan Gum were used in various concentrations. From this formulations batch I12 having HPMC K100 M as main polymer in the concentration of 2% gives sustain drug release as 100.76% for 12 hrs and follows zero order kinetics. Where other polymers *i.e.* HPMC K100 M, Guargum, Xanthan Gum was not able to retain the drug release for 12 hrs in various concentrations.

5. Summary and Conclusion

Hot-melt granulation (HMG) has gained interest in the pharmaceutical field as a processing technology capable of producing solid dispersions with a high degree of drug-polymer interactions. The simultaneous mechanical and thermal shear of samples achieved by HMG can noticeably modify drug properties such as solubility, poor taste, and flow-ability, while producing sustained drug delivery systems.

In the present study *i.e.* formulation and evaluation of floating microencapsulation of Ilaprazole stearic acid, Glyceryl monosterate, Cetyl alcohol were used as base and various polymers like HPMC K100 M, Guargum, Xanthum gum, were used in various concentrations. From this formulations HPMC K100 M in the concentration of 2% (I12) gives sustain drug release as 100.76% for 12 hr and follows zero order kinetics. Where other polymers i;e, Xanthum gum, Guar gum, were not able to retain the drug release for 12 hrs in various concentrations.

References

[1]. Dubey R., Shami T.C. and Bhasker Rao K.U. (2009), Microencapsulation Technology and Applications Defence Science Journal, Vol. 59, No. 1, pp. 82-95

[2]. Patil Hemlata, Tiwari Roshan V., and Michael A. Repka Encapsulation via Hot-Melt Extrusion chapter 15, 213-230.

[3]. Garg Ayush*, Chhipa Kapil and Lalit Kumar (2018) Microencapsulation Techniques in Pharmaceutical Formulation. ejpmr, 5(3), 199-206.

[4]. Jacob S. and Shirwaikar A.1 (2009) Preparation and Evaluation of Microencapsulated Fast Melt Tablets of Ambroxol Hydrochloride Indian Journal of Pharmaceutical Sciences, 276-284.

[5]. *Dr. Kajale A.D., Dr. Gawande S.R., Dr. Bakde B.V., Dr. Channawar M.A, Kude M and Chirde P. Development and Evaluation of Floating Microencapsules of Ilaprazole by Hot Melt Granulation Method World Journal of Pharmacy and Pharmaceutical Sciences Volume 9, Issue 1, 827-838.

[6]. Ghosh SK. Functional coatings and microencapsulation: A general perspective, Ch 1. Wiley-VCH, Verlag GmbH & Co. KGoaA, Weinheim. Green BK. 1960. US Patent Re, 24: 899.

[7]. Modi Dhaval J and Shastri Divyesh H**,** (2011) Fluidized Hot Melt Granulation: Promising Technique for Dissolution Enhancement, Annals of Pharmacology and Pharmaceutics, Annals of Pharmacology and Pharmaceutics, Remedy Publications LLC. 2(18) Article, 1093: 1-3.

[8]. Kukec Simon. (2012) A study of in situ _uid bed melt granulation using response surface methodology. Acta Pharm, 62: 497-513.

[9]. Mašic I, Ilic I, Dreu R, Ibric S, Parojcic J, Duric Z. (2012) Fluidized Hot Melt Granulation. Int J Pharm, 423(2): 202-12.

[10]. Kedar Swarnkar, Tanwar Prasad, Sharma Mukesh Ashok, Singhal Monit, Sharma Ashish, (2012) Preparation and Optimization of Oral Floating Alginate Gel Beads of Famotidine, International Journal of Pharmaceutical Studies and Research, 3(2): 4-8.

[11]. Menon Thulasi V, Sajeeth C.I., (2013) Formulation and Evaluation of Sustained Release Sodium Alginate Microbeads of Carvedilol, International Journal of PharmTechResearch, 5(2): 746-753.

[12]. Muzib Indira, Rekha Ch, (2012) Design and Evaluation of Multi Unit Floating Alginate Beads of Famotidine, International Journal of Pharmacy and Industrial Research, 2(3): 344-353.

[13]. Ansel H.C., Loyd A., Popovich N.G., Pharmaceutical Dosage form and drug delivery system 7th Edition, 60: 179.

[14]. Subrahmanyam CVS, Text book of Physical Pharmaceutics, Vallabh Publication, second edition, 195-206.

[15]. Trishna Bal, Shubhranshu Sengupta, Murthy Padala Narasimha, (2013) Formulation and evaluation of carvedilol microcapsules using Eudragit NE30D and sodium alginate, Brazilian Journal of Pharmaceutical Sciences, 49(4): 889-901.